#29

PATENT
Atty. Docket No.: 1142.0121

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No. 4,758,579)
)
Issued: July 19, 1988)
)
To: Bernhard Kohl, Ernst Sturm,)
Georg Rainer)
)
Assignee: BYK Gulden Lomberg Chemische)
Fabrik GmbH)
)
For: FLUOROALKOXY SUBSTITUTED)
BENZIMIDAZOLES USEFUL AS)
GASTRIC ACID SECRETION)
INHIBITORS)

ATTN: BOX PATENT EXT.
Commissioner for Patents
Washington, D.C. 20231

Sir:

APPLICATION FOR EXTENSION OF PATENT
TERM UNDER 35 U.S.C. § 156

Your Applicant, BYK Gulden Lomberg Chemische Fabrik GmbH, represents that it is the Assignee of the entire interest in and to Letters Patent of the United States 4,758,579 granted to Bernhard Kohl, Ernst Sturm and Georg Rainer on the 19th day of July, 1988, for FLUOROALKOXY SUBSTITUTED BENZIMIDAZOLES USEFUL AS GASTRIC ACID SECRETION INHIBITORS, by virtue of an assignment in favor of BYK Gulden Lomberg Chemische Fabrik GmbH. The assignment to BYK Gulden Lomberg Chemische Fabrik GmbH was recorded on Reel 4430, at Frame 0473, on July 23, 1985. By the Power of Attorney enclosed herein (Attachment A), Applicant appoints

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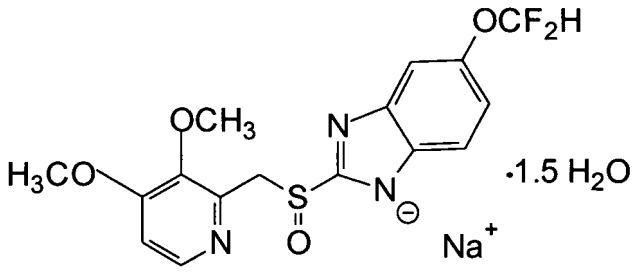
202-408-4000

Egon E. Berg, Rebecca R. Barrett, Steven R. Eck, Arnold S. Milowsky, Michael R. Nagy, George Tarnowski, Daniel Moran and attorneys in Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P., including Charles E. Van Horn, as attorneys for BYK Gulden Lomberg Chemische Fabrik GmbH with regard to this application for extension of the term of U.S. Patent 4,758,579 and to transact all business in the U.S. Patent and Trademark Office in connection therewith.

Applicant hereby submits this application for extension of the patent term under 35 U.S.C. § 156 by providing the following information required by the rules promulgated by the U.S. Patent and Trademark Office (37 C.F.R. § 1.740). For the convenience of the Patent and Trademark Office, the information contained in this application is presented in a format that follows the requirements of Section 1.740 of Title 37 of the Code of Federal Regulations.

(1) The approved product PROTONIX® is pantoprazole sodium, or sodium 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1*H*-benzimidazole in the form of its sesquihydrate. The structural formula of the active ingredient is:



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(2) The approved product was subject to regulatory review under the Federal Food, Drug and Cosmetic Act Section 505.

(3) The approved product PROTONIX® received permission for commercial marketing or use under Section 505 of the Federal Food, Drug and Cosmetic Act on February 2, 2000.

(4) The active ingredient in PROTONIX® is sodium 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1*H*-benzimidazole in the form of its sesquihydrate which, on information and belief, has not been approved for commercial marketing or use under Section 505 of the Federal Food, Drug and Cosmetic Act prior to the approval of NDA 20-987 for PROTONIX® by the Food and Drug Administration on February 2, 2000. A copy of the revised draft labeling describing the approved product is attached (Attachment B).

(5) This application for extension of patent term under 35 U.S.C. § 156 is being submitted within the permitted 60-day period pursuant to 37 C.F.R. § 1.720(f), said period will expire on April 2, 2000.

(6) The complete identification of the patent for which a term extension is being sought is as follows:

Inventors: Bernhard Kohl, Ernst Sturm and Georg Rainer

Patent No.: 4,758,579

Issue Date: July 19, 1988

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Expiration Date: July 19, 2005.

(7) A true copy of the patent is attached (Attachment C).

(8) No terminal disclaimer or reexamination certificate has been issued on this patent. A certificate of correction was issued July 4, 1989, a copy of which is attached to the patent (Attachment C). Copies of the maintenance fee statements indicating payment of maintenance fees in 1991, 1995 and 1999 are attached (Attachment D).

(9) U.S. Patent 4,758,579 claims an active ingredient in the approved product in at least claims 1, 2, 4-6, 8, 18, 20, and 22-28.

The active ingredient is claimed in claim 1 when

R1 is 1C alkyl predominantly substituted by fluorine;

R1' is a hydrogen atom;

R2 is 1C alkoxy;

R3 is 1C alkoxy;

R4 is a hydrogen atom;

n is one;

and the dialkoxypyridine is in the form of a salt.

The active ingredient is claimed in claim 2 when

R1 is 1C alkyl predominantly substituted by fluorine;

R1' is a hydrogen atom;

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R2 is 1C alkoxy;

R3 is 1C alkoxy;

R4 is a hydrogen atom;

n is one;

and the dialkoxypyridine is in the form of a salt.

The active ingredient is claimed in claim 4 when R1' is a hydrogen atom and R1, R2, R3, R4 and n are as defined above with respect to claim 2, and the dialkoxypyridine is in the form of a salt.

The active ingredient is claimed in claim 5 when R1 is difluoromethyl, R1' is a hydrogen atom, R3 is methoxy, R2 is methoxy, R4 is a hydrogen atom, n is 1 and the dialkoxypyridine is in the form of a salt.

The active ingredient is claimed in claim 6 when R1 is difluoromethyl, R1' is a hydrogen atom, R3 is methoxy, R2 is methoxy, R4 is a hydrogen atom, n is 1, and the dialkoxypyridine is in the form of a salt.

The active ingredient is claimed in claim 8 when R4 is a hydrogen atom, R2 and R3 are methoxy, and the dialkoxypyridine is in the form of a salt.

The active ingredient is claimed in claim 18 for the reasons set forth with respect to claim 1.

The active ingredient is claimed in claim 20 for the reasons set forth with respect to claim 1.

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The active ingredient is claimed in claim 22 in the form of a pharmacologically-compatible salt.

The active ingredient is claimed in claim 23 when R1 is difluoromethyl, R1' is a hydrogen atom, R3 is methoxy, R2 is methoxy, R4 is hydrogen, n is 1, and the dialkoxypridine is in the form of a salt.

The active ingredient is claimed in claim 24 when R1 is difluoromethyl, R1' is a hydrogen atom, R3 is methoxy, R2 is methoxy, R4 is hydrogen, n is 1, and the dialkoxypyridine is in the form of a salt.

The active ingredient is claimed in claim 25.

A composition including the active ingredient is claimed in claim 26 for the reasons set forth with respect to claim 20.

Claims 27 and 28 are directed to methods of using the active ingredient for the reasons set forth with respect to claim 20.

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(10) The relevant dates and information pursuant to 35 U.S.C. § 156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

Investigational New Drug Application (IND 35441) for PROTONIX® was submitted September 13, 1990, and became effective on October 13, 1990, 30 days after the date of submission on September 13, 1990.

New Drug Application for PROTONIX® (NDA 20-987) was submitted on June 30, 1998.

New Drug Application for PROTONIX® was approved on February 2, 2000

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(11) A brief description of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to PROTONIX® and the dates applicable to these significant activities are set forth in a chronology of events in Attachment E.

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(12)(i) Applicant is of the opinion that U.S. Patent 4,758,579 is eligible for extension of the patent term under 35 U.S.C. § 156 because it satisfies all requirements for such extension as follows:

(a) 35 U.S.C. § 156(a) - U.S. Patent 4,758,579 claims the product PROTONIX®.

(b) 35 U.S.C. § 156(a)(1) - U.S. Patent 4,758,579 has not expired before submission of this application.

(c) 35 U.S.C. § 156(a)(2) - The term of U.S. Patent 4,758,579 has never been extended under 35 U.S.C. § 156(e)(1).

(d) 35 U.S.C. § 156(a)(3) - The application for extension is submitted by the owner of record of the patent in accordance with the requirements of paragraphs (1) through (4) of 35 U.S.C. § 156(d) and the rules of the Patent and Trademark Office.

(e) 35 U.S.C. § 156(a)(4) - The product PROTONIX® has been subjected to a regulatory review period before its commercial marketing or use.

(f) 35 U.S.C. § 156(a)(5)(A) - The commercial marketing or use of the product PROTONIX® after the regulatory review period is the first permitted commercial marketing or use under the provision of the Federal Food, Drug and Cosmetic Act (i.e., Section 505) under which such regulatory review period occurred.

(g) 35 U.S.C. § 156(c)(4) - No other patent has been extended for the same regulatory review period for the product PROTONIX®.

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(12)(ii) The length of the extension of patent term of U.S. Patent 4,758,579 claimed by Applicant is that period authorized by 35 U.S.C. § 156(c) which has been calculated to be 5 years. The length of the extension was determined pursuant to 37 C.F.R. § 1.775 as follows:

(a) The regulatory review period under 35 U.S.C. § 156(g)(1)(B) began on October 13, 1990 and ended February 2, 2000, which is a total of 3401 days, which is the sum of (1) and (2) below:

(1) The period of review under 35 U.S.C. § 156(g)(1)(B)(i), the "Testing Period", began on October 13, 1990 and ended on June 30, 1998, which is 2818 days; and

(2) The period of review under 35 U.S.C. § 156(g)(1)(B)(ii), the "Approval Period", began on June 30, 1998, and ended on February 2, 2000, which is a total of 583 days.

(b) The regulatory review period upon which the period of extension is calculated is the entire regulatory review period as determined in subparagraph 12(ii)(a) above (3401 days) less:

(1) The number of days in the regulatory review period which were on or before the date on which the patent issued (July 19, 1988) which is zero (0) days; and

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(2) The number of days during which applicant did not act with due diligence, which is zero (0) days; and

(3) One-half the number of days determined in sub-paragraph (12)(ii)(a)(1) above after the patent issued (one-half of 2818 days) which is 1409 days;

(c) The number of days as determined in sub-paragraph (12)(ii)(b) (1992 days) when added to the expiration date of the original term of the patent (July 19, 2005) would result in the date of January 1, 2011;

(d) Fourteen (14) years when added to the date of the NDA approval (February 2, 2000) would result in the date of February 2, 2014;

(e) The earlier date as determined in sub-paragraphs (12)(ii)(c) and (12)(ii)(d) is January 1, 2011;

(f) Since U.S. Patent 4,758,579 issued after September 24, 1984, the period of extension may not exceed five years from the original expiration date of July 19, 2005. Five years when added to the original expiration date of the patent would result in the date of July 19, 2010.

(g) The earlier dates as determined by sub-paragraph (12)(ii)(e) and (12)(ii)(f) is July 19, 2010.

(13) Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any

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information which is material to the determination of entitlement to the extension sought.

(14) The prescribed fee for receiving and acting upon this application is attached as a check in the amount of $1,120.00. The Commissioner is authorized to charge any additional fees required by this application to Deposit Account No. 06-0916.

(15) All correspondence and inquiries may be directed to the undersigned, whose address, telephone number and fax number are as follows:

Charles E. Van Horn

Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.

1300 I Street, N.W.

Washington, D.C. 20005-3315

Phone: 202-408-4000

Fax: 202-408-4400

(16) Enclosed is a certification that the application for extension of patent term under 35 U.S.C. § 156 including its attachments and supporting papers is being submitted as one original and four (4) copies thereof (Attachment F).

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(17) The requisite declaration pursuant to 37 C.F.R. § 1.740(b) is attached (Attachment G).

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

By: Charles E Van Horn
Charles E. Van Horn
Reg. No. 40,266

Date: March 28, 2000

Attachments
Power of Attorney (Attachment A)
Package Insert for PROTONIX® (Attachment B)
U.S. Patent 4,758,579 (Attachment C)
Copy of Maintenance Fee Statements (Attachment D)
Chronology of Regulatory Review Period (Attachment E)
Certification of Copies of Application Papers (Attachment F)
Declaration Pursuant to 37 C.F.R. § 1.740(b) (Attachment G)

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ATTN: BOX PATENT EXTENSION

A

PATENT
Atty. Docket No.: 1142.0121

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No. 4,758,579)
)
Issued: July 19, 1988)
)
To: Bernhard Kohl, Ernst Sturm)
Georg Rainer)
)
Assignee: BYK Gulden Lomberg Chemische)
Fabrik GmbH)
)
For: FLUOROALKOXY SUBSTITUTED)
BENZIMIDAZOLES USEFUL AS)
GASTRIC ACID SECRETION)
INHIBITORS)

ATTN: BOX PATENT EXTENSION
Commissioner for Patents
Washington, D.C. 20231

Sir:

POWER OF ATTORNEY

BYK Gulden Lomberg Chemische Fabrik GmbH is the Assignee of the entire right, title, and interest in the patent identified above by virtue of an assignment recorded in the Patent and Trademark Office at Reel 4430, at Frame 0473 on July 23, 1985.

Assignee, BYK Gulden Lomberg Chemische Fabrik GmbH, being the owner of the above-identified U.S. Letters Patent, hereby grants the power of attorney to Egon E. Berg, Reg. No. 21,117; Rebecca R. Barrett, Reg. No. 35,152; Steven R. Eck, Reg. No. 36,126; Arnold S. Milowsky, Reg. No. 35,288; Michael R. Nagy, Reg. No. 33,432;

George Tarnowski, Reg. No. 27,472; Daniel B. Moran, Reg. No. 41,204; and to **FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.**, Douglas B. Henderson, Reg. No. 20,291; Ford F. Farabow, Jr., Reg. No. 20,630; Arthur S. Garrett, Reg. No. 20,338; Donald R. Dunner, Reg. No. 19,073; Brian G. Brunsvold, Reg. No. 22,593; Tipton D. Jennings, IV, Reg. No. 20,645; Jerry D. Voight, Reg. No. 23,020; Laurence R. Hefter, Reg. No. 20,827; Kenneth E. Payne, Reg. No. 23,098; Herbert H. Mintz, Reg. No. 26,691; C. Larry O'Rourke, Reg. No. 26,014; Albert J. Santorelli, Reg. No. 22,610; Michael C. Elmer, Reg. No. 25,857; Richard H. Smith, Reg. No. 20,609; Stephen L. Peterson, Reg. No. 26,325; John M. Romary, Reg. No. 26,331; Bruce C. Zotter, Reg. No. 27,680; Dennis P. O'Reilley, Reg. No. 27,932; Allen M. Sokal, Reg. No. 26,695; Robert D. Bajefsky, Reg. No. 25,387; Richard L. Stroup, Reg. No. 28,478; David W. Hill, Reg. No. 28,220; Thomas L. Irving, Reg. No. 28,619; Charles E. Lipsey, Reg. No. 28,165; Thomas W. Winland, Reg. No. 27,605; Basil J. Lewris, Reg. No. 28,818; Martin I. Fuchs, Reg. No. 28,508; E. Robert Yoches, Reg. No. 30,120; Barry W. Graham, Reg. No. 29,924; Susan Haberman Griffen, Reg. No. 30,907; Richard B. Racine, Reg. No. 30,415; Thomas H. Jenkins, Reg. No. 30,857; Robert E. Converse, Jr., Reg. No. 27,432; Clair X. Mullen, Jr., Reg. No. 20,348; Christopher P. Foley, Reg. No. 31,354; John C. Paul, Reg. No. 30,413; Roger D. Taylor, Reg. No. 28,992; David M. Kelly, Reg. No. 30,953; Kenneth J. Meyers, Reg. No. 25,146; Carol P. Einaudi, Reg. No. 32,220; Walter Y. Boyd, Jr., Reg. No. 31,738; Steven M. Anzalone, Reg. No.

32,095; Jean B. Fordis, Reg. No. 32,984; Barbara C. McCurdy, Reg. No. 32,120; James K. Hammond, Reg. No. 31,964; Richard V. Burgujian, Reg. No. 31,744; J. Michael Jakes, Reg. No. 32,824; Thomas W. Banks, Reg. No. 32,719; Christopher P. Isaac, Reg. No. 32,616; Bryan C. Diner, Reg. No. 32,409; M. Paul Barker, Reg. No. 32,013; Andrew Chanho Sonu, Reg. No. 33,457; David S. Forman, Reg. No. 33,694; Vincent P. Kovalick, Reg. No. 32,867; James W. Edmondson, Reg. No. 33,871; Michael R. McGurk, Reg. No. 32,045; Joann M. Neth, Reg. No. 36,363; Gerson S. Panitch, Reg. No. 33,751; Cheri M. Taylor, Reg. No. 33,216; Charles E. Van Horn, Reg. No. 40,266; Linda A. Wadler, Reg. No. 33,218; Jeffrey A. Berkowitz, Reg. No. 36,743; Michael R. Kelly, Reg. No. 33,921; James B. Monroe, Reg. No. 33,971; Doris Johnson Hines, Reg. No. 34,629; Allen R. Jensen, Reg. No. 28,224; Lori Ann Johnson, Reg. No. 34,498; and David A. Manspeizer, Reg. No. 37,540, both jointly and separately to be attorneys for BYK Gulden Lomberg Chemische Fabrik GmbH with regard to an application for extension of the term of U.S. Patent 4,758,579 and to transact all business in the Patent and Trademark Office connected therewith.

The undersigned is empowered to act on behalf of the Assignee.

Please send all future correspondence concerning the above matter to

Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P., at the following address:

Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.
1300 I Street, N.W.
Washington, D.C. 20005-3315

BYK Gulden Lomberg Chemische Fabrik GmbH

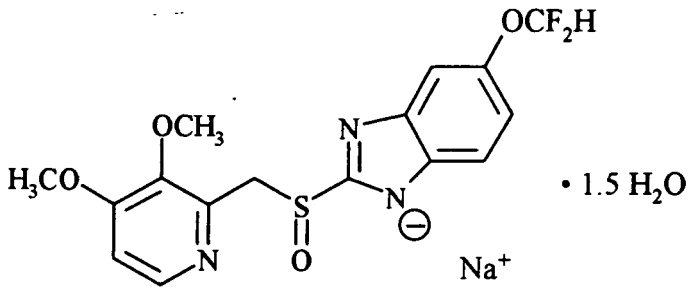
Date: 22 March 2000

ppa.Dr.Herbert Suchy
Authorized Officer

i.V.Dr.Ulrich Wolf
Head of Patent Department

DESCRIPTION

The active ingredient in PROTONIX® (pantoprazole sodium) Delayed-Release Tablets is a substituted benzimidazole, sodium 5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl)methyl] sulfinyl]-1*H*-benzimidazole sesquihydrate, a compound that inhibits gastric acid secretion. Its empirical formula is $C_{16}H_{14}F_2N_3NaO_4S$ x 1.5 H_2O, with a molecular weight of 432.4. The structural formula is:



Pantoprazole sodium sesquihydrate is a white to off-white crystalline powder and is racemic. Pantoprazole has weakly basic and acidic properties. Pantoprazole sodium sesquihydrate is freely soluble in water, very slightly soluble in phosphate buffer at pH 7.4, and practically insoluble in n-hexane.

The stability of the compound in aqueous solution is pH-dependent. The rate of degradation increases with decreasing pH. At ambient temperature, the degradation half-life is approximately 2.8 hours at pH 5.0 and approximately 220 hours at pH 7.8.

PROTONIX is supplied as a delayed-release tablet for oral administration. Each delayed-release tablet contains 45.1 mg of pantoprazole sodium sesquihydrate (equivalent to 40 mg pantoprazole) with the following inactive ingredients: anhydrous sodium carbonate NF, mannitol USP, crospovidone NF, povidone USP, calcium stearate NF, hydroxypropyl methylcellulose USP, titanium dioxide USP, yellow iron oxide NF, propylene glycol USP, methacrylic acid copolymer NF, polysorbate 80 NF, sodium lauryl sulfate NF, and triethyl citrate NF.

CLINICAL PHARMACOLOGY

Pharmacokinetics

PROTONIX is prepared as an enteric-coated tablet so that absorption of pantoprazole begins only after the tablet leaves the stomach. Peak serum concentration (C_{max}) and area under the serum concentration time curve (AUC) increase in a manner proportional to oral and intravenous doses from 10 mg to 80 mg. Pantoprazole does not accumulate and its pharmacokinetics are unaltered with multiple daily dosing. Following oral or intravenous administration, the serum concentration of pantoprazole declines biexponentially with a terminal elimination half-life of approximately one hour. In extensive metabolizers (see Metabolism section) with normal liver function receiving an oral dose of the enteric-coated 40 mg pantoprazole tablet, the peak concentration (C_{max}) is 2.4 µg/mL, the time to reach the peak concentration (t_{max}) is 2.4 h and the total area under the plasma concentration versus time curve (AUC) is 4.8 µg·hr/mL. When pantoprazole is given with food, its t_{max} is highly variable and may increase significantly.

Following intravenous administration of pantoprazole to extensive metabolizers, its total clearance is 7.6-14.0 L/h and its apparent volume of distribution is 11.0-23.6L.

Absorption

The absorption of pantoprazole is rapid, with a C_{max} of 2.5 µg/mL that occurs approximately 2.5 hours after single or multiple oral 40-mg doses. Pantoprazole is well absorbed; it undergoes little first-pass metabolism resulting in an absolute bioavailability of approximately 77%. Pantoprazole absorption is not affected by concomitant administration of antacids. Administration of pantoprazole with food may delay its absorption up to 2 hours or longer; however, the C_{max} and the extent of pantoprazole absorption (AUC) are not altered. Thus, pantoprazole may be taken without regard to timing of meals.

Distribution

The apparent volume of distribution of pantoprazole is approximately 11.0-23.6L, distributing mainly in extracellular fluid. The serum protein binding of pantoprazole is about 98%, primarily to albumin.

Metabolism

Pantoprazole is extensively metabolized in the liver through the cytochrome P450 (CYP) system. Pantoprazole metabolism is independent of the route of administration (intravenous or oral). The main metabolic pathway is demethylation, by CYP2C19, with subsequent sulfation; other metabolic pathways include oxidation by CYP3A4. There is no evidence that any of the pantoprazole metabolites have significant pharmacologic activity. CYP2C19 displays a known genetic polymorphism due to its deficiency in some sub-populations (e.g. 3% of Caucasians and African-Americans and 17-23% of Asians). Although these sub-populations of slow pantoprazole metabolizers have elimination half-life values of 3.5 to 10.0 hours, they still have minimal accumulation (≤ 23%) with once daily dosing.

Elimination

After a single oral or intravenous dose of ^{14}C-labeled pantoprazole to healthy, normal metabolizer volunteers, approximately 71% of the dose was excreted in the urine with 18% excreted in the feces through biliary excretion. There was no renal excretion of unchanged pantoprazole.

Special Populations

Geriatric

Only slight to moderate increases in pantoprazole AUC (43%) and C_{max} (26%) were found in elderly volunteers (64 to 76 years of age) after repeated oral administration, compared with younger subjects. No dosage adjustment is recommended based on age.

Pediatric

The pharmacokinetics of pantoprazole have not been investigated in patients <18 years of age.

Gender

There is a modest increase in pantoprazole AUC and C_{max} in women compared to men. However, weight-normalized clearance values are similar in women and men. No dosage adjustment is needed based on gender (Also see Use in Women).

Renal Impairment

In patients with severe renal impairment, pharmacokinetic parameters for pantoprazole were similar to those of healthy subjects. No dosage adjustment is necessary in patients with renal impairment or in patients undergoing hemodialysis.

Hepatic Impairment

In patients with mild to moderate hepatic impairment, maximum pantoprazole concentrations increased only slightly (1.5-fold) relative to healthy subjects. Although serum half-life values increased to 7-9 hours and AUC values increased by 5- to 7-fold in hepatic-impaired patients, these increases were no greater than those observed in slow CYP2C19 metabolizers, where no dosage frequency adjustment is warranted. These pharmacokinetic changes in hepatic-impaired patients result in minimal drug accumulation following once daily multiple-dose administration. No dosage adjustment is needed in patients with mild or moderate hepatic impairment. The pharmacokinetics of pantoprazole have not yet been well characterized in patients with severe hepatic impairment. Therefore, the potential for modest drug accumulation (≤ 21%) when dosed once daily needs to be weighed against the potential for reduced acid control when dosed every other day in these patients.

Drug-Drug Interactions

Pantoprazole is metabolized mainly by CYP2C19 and to minor extents by CYPs 3A4, 2D6 and 2C9. In *in vivo* drug-drug interaction studies with CYP2C19 substrates (diazepam [also a CYP3A4 substrate] and phenytoin [also a CYP3A4 inducer]), nifedipine (a CYP3A4 substrate), metoprolol (a CYP2D6 substrate), diclofenac (a CYP2C9 substrate) and theophylline (a CYP1A2 substrate) in healthy subjects, the pharmacokinetics of pantoprazole were not significantly altered. It is, therefore, expected that other drugs metabolized by CYPs 2C19, 3A4, 2D6, 2C9 and 1A2 would not significantly affect the pharmacokinetics of pantoprazole. *In vivo* studies also suggest that pantoprazole does not significantly affect the kinetics of other drugs (cisapride, theophylline, diazepam [and its active metabolite, desmethyldiazepam], phenytoin, warfarin, metoprolol, nifedipine, carbamazepine and oral contraceptives) metabolized by CYPs 2C19, 3A4, 2C9, 2D6 and 1A2. Therefore, it is expected that pantoprazole would not significantly affect the pharmacokinetics of other drugs metabolized by these isozymes. Dosage adjustment of such drugs is not necessary when they are co-administered with pantoprazole. In other *in vivo* studies, digoxin, ethanol, glyburide, antipyrine, and caffeine had no clinically relevant interactions with pantoprazole.

Pharmacodynamics

Mechanism of Action

Pantoprazole is a proton pump inhibitor (PPI) that suppresses the final step in gastric acid production by forming a covalent bond to two sites of the (H^+,K^+)-ATPase enzyme system at the secretory surface of the gastric parietal cell. This effect is dose-related and leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus. The binding to the (H^+,K^+)-ATPase results in a duration of antisecretory effect that persists longer than 24 hours.

Antisecretory Activity

Under maximal acid stimulatory conditions using pentagastrin, a dose-dependent decrease in gastric acid output occurs after a single dose of oral (20-80 mg) or a single dose of intravenous (20-120 mg) pantoprazole in healthy volunteers. Pantoprazole given once daily results in increasing inhibition of gastric acid secretion. Following the initial oral dose of 40 mg pantoprazole, a 51% mean inhibition was achieved by 2.5 hours. With once a day dosing for 7 days the mean inhibition was increased to 85%. Pantoprazole suppressed acid secretion in excess of 95% in half of the subjects. Acid secretion had returned to normal within a week after the last dose of pantoprazole; there was no evidence of rebound hypersecretion.

In a series of dose-response studies pantoprazole, at oral doses ranging from 20 to 120 mg, caused dose-related increases in median basal gastric pH and in the percent of time gastric pH was > 3 and > 4. Treatment with 40 mg of pantoprazole produced optimal increases in gastric pH which were significantly greater than the 20-mg dose. Doses higher than 40 mg (60, 80, 120 mg) did not result in further significant increases in median gastric pH. The effects of pantoprazole on median pH from one double-blind crossover study are shown below.

Effect of Single Doses of Oral Pantoprazole on Intragastric pH

	Median pH			
Time	Placebo	20 mg	40 mg	80 mg
8 a.m. - 8 a.m. (24 hours)	1.3	2.9*	3.8*#	3.9*#
8 a.m. - 10 p.m. (Daytime)	1.6	3.2*	4.4*#	4.8*#
10 p.m. - 8 a.m. (Nighttime)	1.2	2.1*	3.0*	2.6*

* Significantly different from placebo
\# Significantly different from 20 mg

A double-blind crossover study compared pantoprazole 40 mg with omeprazole 20 mg once daily for 7 days. For both one day and one week treatment periods, pantoprazole administered in the morning produced significantly greater increases in median pH during 24 hours than did omeprazole.

Serum Gastrin Effects

Fasting serum gastrin levels were assessed in two double-blind studies of the acute healing of erosive esophagitis (EE) in which 682 patients with gastroesophageal reflux disease (GERD) received 10, 20, or 40 mg of pantoprazole for up to 8 weeks. At 4 weeks of treatment there was an increase in mean gastrin levels of 7%, 35%, and 72% over pretreatment values in the 10, 20 and 40 mg treatment groups, respectively. A similar increase in serum gastrin levels was noted at

the 8 week visit with mean increases of 3%, 26%, and 84% for the three pantoprazole dose groups.

In long term studies involving over 800 patients, a 2- to 3-fold mean increase from the pretreatment fasting serum gastrin level was observed in the initial months of treatment with pantoprazole at doses of 40 mg per day during GERD maintenance studies and 40 mg or higher per day in patients with refractory GERD. Fasting serum gastrin levels generally remained at approximately 2 to 3 times baseline for up to 4 years of periodic follow-up in clinical trials.

Following healing of gastric or duodenal ulcers with pantoprazole treatment, elevated gastrin levels return to normal by at least 3 months.

Enterochromaffin-Like (ECL) Cell Effects

In 39 patients treated with oral pantoprazole 40 mg to 240 mg daily (majority receiving 40 mg to 80 mg) for up to 5 years, there was a moderate increase in ECL-cell density starting after the first year of use which appeared to plateau after 4 years.

In a nonclinical study in Sprague-Dawley rats, lifetime exposure (24 months) to pantoprazole at doses of 0.5 to 200 mg/kg/day resulted in dose-related increases in gastric ECL-cell proliferation and gastric neuroendocrine (NE)-cell tumors. Gastric NE-cell tumors in rats may result from chronic elevation of serum gastrin levels. The high density of ECL cells in the rat stomach makes this species highly susceptible to the proliferative effects of elevated gastrin levels produced by proton pump inhibitors. However, there were no observed elevations in serum gastrin following the administration of pantoprazole at a dose of 0.5 mg/kg/day. In a separate study, a gastric NE-cell tumor without concomitant ECL-cell proliferative changes was observed in 1 female rat following 12 months of dosing with pantoprazole at 5 mg/kg/day and a 9 month off-dose recovery. (See **PRECAUTIONS**, Carcinogenesis, Mutagenesis, Impairment of Fertility).

Other Effects

No clinically relevant effects of pantoprazole on cardiovascular, respiratory, ophthalmic, or central nervous system function have been detected. In a clinical pharmacology study, pantoprazole 40 mg given once daily for 2 weeks had no effect on the levels of the following hormones: cortisol, testosterone, triiodothyronine (T3), thyroxine (T4), thyroid-stimulating hormone, thyronine-binding protein, parathyroid hormone, insulin, glucagon, renin, aldosterone, follicle-stimulating hormone, luteinizing hormone, prolactin and growth hormone.

Clinical Studies

PROTONIX Delayed-Release Tablets were used in all clinical trials.

Erosive Esophagitis (EE) Associated with Gastroesophageal Reflux Disease (GERD)

A US multicenter double-blind, placebo-controlled study of PROTONIX 10 mg, 20 mg or 40 mg once daily was conducted in 603 patients with reflux symptoms and endoscopically diagnosed EE of grade 2 or above (Hetzel-Dent scale). In this study, approximately 25% of enrolled patients had severe EE of grade 3 and 10% had grade 4. The percentages of patients healed (per protocol, n=541) in this study were as follows:

Erosive Esophagitis Healing Rates (per protocol)

	PROTONIX			Placebo
Week	10 mg QD (n = 153)	20 mg QD (n = 158)	40 mg QD (n = 162)	(n =68)
4	45.6%[+]	58.4%[+#]	75.0%[+*]	14.3%
8	66.0%[+]	83.5 %[+#]	92.6%[+*]	39.7%

+($p < 0.001$) PROTONIX versus placebo.
*($p < 0.05$) versus 10 mg, or 20 mg PROTONIX
($p < 0.05$) versus 10 mg PROTONIX

In this study, all PROTONIX treatment groups had significantly greater healing rates than the placebo group. This was true regardless of *H. pylori* status for the 20-mg and 40-mg PROTONIX treatment groups. The 40-mg dose of PROTONIX resulted in healing rates significantly greater than those found with either the 20- or 10-mg dose.

A significantly greater proportion of patients taking PROTONIX 40 mg experienced complete relief of daytime and nighttime heartburn and the absence of regurgitation starting from the first day of treatment compared with placebo. Patients taking PROTONIX consumed significantly fewer antacid tablets per day than those taking placebo.

PROTONIX 20 mg and 40 mg once daily was also compared with nizatidine 150 mg twice daily in a US multicenter, double-blind study of 243 patients with reflux symptoms and endoscopically diagnosed EE of grade 2 or above. The percentages of patients healed (per protocol, n=212) were as follows:

Erosive Esophagitis Healing Rates (per protocol)

	PROTONIX		Nizatidine
Week	20 mg QD (n = 72)	40 mg QD (n = 70)	150 mg BID (n = 70)
4	61.4%[+]	64.0%[+]	22.2%
8	79.2%[+]	82.9%[+]	41.4%

[+]($p < 0.001$) PROTONIX versus nizatidine.

Once daily treatment with PROTONIX 20 or 40 mg resulted in significantly superior rates of healing at both 4 and 8 weeks compared with twice daily treatment with 150 mg of nizatidine. For the 40 mg treatment group, significantly greater healing rates compared to nizatidine were achieved regardless of the *H. pylori* status.

A significantly greater proportion of the patients in the PROTONIX treatment groups experienced complete relief of nighttime heartburn and regurgitation starting on the first day and of daytime heartburn on the second day compared with those taking nizatidine 150 mg twice daily. Patients taking PROTONIX consumed significantly fewer antacid tablets per day than those taking nizatidine.

INDICATIONS AND USAGE

Short-Term Treatment of Erosive Esophagitis Associated With Gastroesophageal Reflux Disease (GERD)

PROTONIX Delayed-Release Tablets are indicated for the short-term treatment (up to 8 weeks) in the healing and symptomatic relief of erosive esophagitis. For those patients who have not healed after 8 weeks of treatment, an additional 8 week course of PROTONIX may be considered.

The safety and efficacy of PROTONIX for maintenance therapy (e.g., beyond 16 weeks) have not been established. (see **PRECAUTIONS**).

CONTRAINDICATIONS

PROTONIX Delayed-Release Tablets are contraindicated in patients with known hypersensitivity to any component of the formulation.

PRECAUTIONS

General

Symptomatic response to therapy with pantoprazole does not preclude the presence of gastric malignancy.

In rodents, pantoprazole is carcinogenic and caused rare types of gastrointestinal tumors. The relevance of these animal findings to humans is unknown. The safety and efficacy of PROTONIX for maintenance therapy (e.g., beyond 16 weeks) have not been established. PROTONIX is not indicated for maintenance therapy (see **INDICATIONS AND USAGE**).

No dosage adjustment is necessary in patients with mild or moderate hepatic impairment. The pharmacokinetics of pantoprazole has not been well characterized in patients with severe hepatic impairment. Therefore, the potential for modest drug accumulation ($\leq 21\%$) when dosed once daily needs to be weighed against the potential for reduced acid control when dosed every other day in these patients.

Information for Patients

Patients should be cautioned that PROTONIX Delayed-Release Tablets should not be split, crushed or chewed. The tablets should be swallowed whole, with or without food in the stomach. Concomitant administration of antacids does not affect the absorption of pantoprazole.

Drug Interactions

Pantoprazole is metabolized through the cytochrome P450 system, primarily the CYP2C19 and CYP3A4 isozymes, and subsequently undergoes Phase II conjugation. Based on studies evaluating possible interactions of pantoprazole with other drugs metabolized by the cytochrome P450 system, no dosage adjustment is needed with concomitant use of the following drugs: theophylline, cisapride, antipyrine, caffeine, carbamazepine, diazepam, diclofenac, digoxin, ethanol, glyburide, an oral contraceptive (levonorgestrel/ethinyl estradiol), metoprolol, nifedipine, phenytoin, or warfarin. Clinically relevant interactions of pantoprazole with other drugs with the same metabolic pathways are not expected. Therefore, when co-administered with pantoprazole, adjustment of the dosage of pantoprazole or of such drugs may not be necessary. There was also no interaction with concomitantly administered antacids.

Because of profound and long lasting inhibition of gastric acid secretion, it is theoretically possible that pantoprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (e.g., ketoconazole, ampicillin esters, and iron salts).

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 24-month carcinogenicity study, Sprague-Dawley rats were treated orally with doses of 0.5 to 200 mg/kg/day, about 0.1 to 40 times the exposure on a body surface area basis, of a 50-kg person dosed at 40 mg/day. In the gastric fundus, treatment at 0.5 to 200 mg/kg/day produced enterochromaffin-like (ECL) cell hyperplasia and benign and malignant neuroendocrine cell tumors in a dose-related manner. In the forestomach, treatment at 50 and 200 mg/kg/day (about 10 and 40 times the recommended human dose on a body surface area basis) produced benign squamous cell papillomas and malignant squamous cell carcinomas. Rare gastrointestinal tumors associated with pantoprazole treatment included an adenocarcinoma of the duodenum at 50 mg/kg/day, and benign polyps and adenocarcinomas of the gastric fundus at 200 mg/kg/day. In the liver, treatment at 0.5 to 200 mg/kg/day produced dose-related increases in the incidences of hepatocellular adenomas and carcinomas. In the thyroid gland, treatment at 200 mg/kg/day produced increased incidences of follicular cell adenomas and carcinomas for both male and female rats.

Sporadic occurrences of hepatocellular adenomas and a hepatocellular carcinoma were observed in Sprague-Dawley rats exposed to pantoprazole in 6-month and 12-month toxicity studies.

In a 24-month carcinogenicity study, Fischer 344 rats were treated orally with doses of 5 to 50 mg/kg/day, approximately 1 to 10 times the recommended human dose based on body surface area. In the gastric fundus, treatment at 5 to 50 mg/kg/day produced enterochromaffin-like (ECL) cell hyperplasia and benign and malignant neuroendocrine cell tumors. Dose selection for this study may not have been adequate to comprehensively evaluate the carcinogenic potential of pantoprazole.

In a 24-month carcinogenicity study, B6C3F1 mice were treated orally with doses of 5 to 150 mg/kg/day, 0.5 to 15 times the recommended human dose based on body surface area. In the liver, treatment at 150 mg/kg/day produced increased incidences of combined hepatocellular

adenomas and carcinomas in female mice. Treatment at 5 to 150 mg/kg/day also produced gastric fundic ECL cell hyperplasia.

Pantoprazole was positive in the *in vitro* human lymphocyte chromosomal aberration assays, in one of two mouse micronucleus tests for clastogenic effects, and in the *in vitro* Chinese hamster ovarian cell/HGPRT forward mutation assay for mutagenic effects. Equivocal results were observed in the *in vivo* rat liver DNA covalent binding assay. Pantoprazole was negative in the *in vitro* Ames mutation assay, the *in vitro* unscheduled DNA synthesis (UDS) assay with rat hepatocytes, the *in vitro* AS52/GPT mammalian cell-forward-gene mutation assay, the *in vitro* thymidine kinase mutation test with mouse lymphoma L5178Y cells, and the *in vivo* rat bone marrow cell chromosomal aberration assay.

Pantoprazole at oral doses up to 500 mg/kg/day in male rats (98 times the recommended human dose based on body surface area) and 450 mg/kg/day in female rats (88 times the recommended human dose based on body surface area) was found to have no effect on fertility and reproductive performance.

Pregnancy
Teratogenic Effects
Pregnancy Category B

Teratology studies have been performed in rats at oral doses up to 450 mg/kg/day (88 times the recommended human dose based on body surface area) and rabbits at oral doses up to 40 mg/kg/day (16 times the recommended human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to pantoprazole. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Pantoprazole and its metabolites are excreted in the milk of rats. It is not known whether pantoprazole is excreted in human milk. Many drugs which are excreted in human milk have a potential for serious adverse reactions in nursing infants. Based on the potential for tumorigenicity shown for pantoprazole in rodent carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the benefit of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Use in Women

Erosive esophagitis healing rates in the 221 women treated with pantoprazole in US clinical trials were similar to those found in men. The incidence rates of adverse events were also similar between men and women.

Use in Elderly

Erosive esophagitis healing rates in the 107 elderly patients (≥65 years old) treated with pantoprazole in US clinical trials were similar to those found in patients under the age of 65. The incidence rates of adverse events and laboratory abnormalities in patients aged 65 years and older were similar to those associated with patients younger than 65 years of age. The healing rates of the 25 patients at least 75 years old were 80% for those treated with 10 mg of pantoprazole and 100% for those patients treated with either 20 or 40 mg. In addition, the safety profile in patients 65 years and older was similar to that of patients younger than 65 years of age.

ADVERSE REACTIONS

Worldwide, more than 11,100 patients have been treated with pantoprazole in clinical trials involving various dosages and duration of treatment. In general, pantoprazole has been well tolerated in both short-term and long-term trials.

In two US controlled clinical trials involving PROTONIX 10-, 20-, or 40-mg doses for up to 8 weeks, there were no dose-related effects on the incidence of adverse events. The following adverse events considered by investigators to be possibly, probably or definitely related to drug occurred in 1% or more in the individual studies of GERD patients on therapy with PROTONIX.

Most Frequent Adverse Events Reported as Drug Related in Short-term Domestic Trials

	% Incidence			
	Study 300-US		**Study 301-US**	
Study Event	PROTONIX (n = 521)	Placebo (n = 82)	PROTONIX (n = 161)	Nizatidine (n = 82)
Headache	6	6	9	13
Diarrhea	4	1	6	6
Flatulence	2	2	4	0
Abdominal pain	1	2	4	4
Rash	<1	0	2	0
Eructation	1	1	0	0
Insomnia	<1	2	1	1
Hyperglycemia	1	0	<1	0

Note: Only adverse events with an incidence greater than or equal to the comparators are shown.

In addition, in these short-term domestic trials, the following treatment-emergent events, regardless of causality, occurred at a rate of ≥ 1% in PROTONIX-treated patients: asthenia, back pain, chest pain, neck pain, flu syndrome, infection, pain, migraine, constipation, dyspepsia, gastroenteritis, gastrointestinal disorder, nausea, rectal disorder, vomiting, hyperlipemia, liver function tests abnormal, SGPT increased, arthralgia, anxiety, dizziness, hypertonia, bronchitis, cough increased, dyspnea, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection, urinary frequency, and urinary tract infection.

In international short-term double-blind or open-label, clinical trials involving 20- to 80 mg per day, the following adverse events were reported to occur in 1% or more of 2805 GERD patients receiving pantoprazole for up to 8 weeks.

Adverse Events in GERD Patients in Short-term International Trials

	% Incidence			
Study Event	Pantoprazole Total (N=2805)	Ranitidine 300 mg (N=594)	Omeprazole 20 mg (N=474)	Famotidine 40 mg (N=239)
Headache	2	3	2	1
Diarrhea	2	2	2	<1
Abdominal Pain	1	1	<1	<1

Additional adverse experiences occurring in <1% of GERD patients based on pooled results from either short-term domestic or international trials are shown below within each body system. In most instances the relationship to pantoprazole was unclear.

BODY AS A WHOLE: abscess, allergic reaction, chills, cyst, face edema, fever, generalized edema, heat stroke, hernia, laboratory test abnormal, malaise, moniliasis, neoplasm, non-specified drug reaction.

CARDIOVASCULAR SYSTEM: angina pectoris, arrhythmia, cardiovascular disorder, chest pain substernal, congestive heart failure, electrocardiogram abnormal, hemorrhage, hypertension, hypotension, myocardial ischemia, palpitation, retinal vascular disorder, syncope, tachycardia, thrombophlebitis, thrombosis, vasodilatation.

DIGESTIVE SYSTEM: anorexia, aphthous stomatitis, cardiospasm, colitis, dry mouth, duodenitis, dysphagia, enteritis, esophageal hemorrhage, esophagitis, gastrointestinal carcinoma, gastrointestinal hemorrhage, gastrointestinal moniliasis, gingivitis, glossitis, halitosis, hematemesis, increased appetite, melena, mouth ulceration, oral moniliasis, periodontal abscess, periodontitis, rectal hemorrhage, stomach ulcer, stomatitis, stools abnormal, tongue discoloration, ulcerative colitis.

ENDOCRINE SYSTEM: diabetes mellitus, glycosuria, goiter.

HEPATO-BILIARY SYSTEM: biliary pain, bilirubinemia, cholecystitis, cholelithiasis, cholestatic jaundice, hepatitis, alkaline phosphatase increased, gamma glutamyl transpeptidase increased, SGOT increased.

HEMIC AND LYMPHATIC SYSTEM: anemia, ecchymosis, eosinophilia, hypochromic anemia, iron deficiency anemia, leukocytosis, leukopenia, thrombocytopenia.

METABOLIC AND NUTRITIONAL: dehydration, edema, gout, peripheral edema, thirst, weight gain, weight loss.

MUSCULOSKELETAL SYSTEM: arthritis, arthrosis, bone disorder, bone pain, bursitis, joint disorder, leg cramps, neck rigidity, myalgia, tenosynovitis.

NERVOUS SYSTEM: abnormal dreams, confusion, convulsion, depression, dry mouth, dysarthria, emotional lability, hallucinations, hyperkinesia, hypesthesia, libido decreased,

nervousness, neuralgia, neuritis, paresthesia, reflexes decreased, sleep disorder, somnolence, thinking abnormal, tremor, vertigo.

RESPIRATORY SYSTEM: asthma, epistaxis, hiccup, laryngitis, lung disorder, pneumonia, voice alteration.

SKIN AND APPENDAGES: acne, alopecia, contact dermatitis, dry skin, eczema, fungal dermatitis, hemorrhage, herpes simplex, herpes zoster, lichenoid dermatitis, maculopapular rash, pain, pruritus, skin disorder, skin ulcer, sweating, urticaria.

SPECIAL SENSES: abnormal vision, amblyopia, cataract specified, deafness, diplopia, ear pain, extraocular palsy, glaucoma, otitis externa, taste perversion, tinnitus.

UROGENITAL SYSTEM: albuminuria, balanitis, breast pain, cystitis, dysmenorrhea, dysuria, epididymitis, hematuria, impotence, kidney calculus, kidney pain, nocturia, prostatic disorder, pyelonephritis, scrotal edema, urethral pain, urethritis, urinary tract disorder, urination impaired, vaginitis.

Postmarketing Reports

There have been spontaneous reports of adverse events with the post-marketing use of pantoprazole. These reports include anaphylaxis; angioedema (Quincke's edema); anterior ischemic optic neuropathy; severe dematologic reactions, including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis (TEN, some fatal); and pancreatitis.

In addition, also observed have been jaundice, confusion, hypokinesia, speech disorder, increased salivation, vertigo, nausea, and tinnitus.

Laboratory Values

In two US controlled trials, 0.4 % of the patients on 40 mg pantoprazole experienced SGPT elevations of greater than three times the upper limit of normal at the final treatment visit. Except in those patients where there was a clear alternative explanation for a laboratory value change, such as intercurrent illness, the elevations tended to be mild and sporadic. The following changes in laboratory parameters were reported as adverse events: creatinine increased, hypercholesterolemia, and hyperuricemia.

OVERDOSAGE

Some reports of overdosage with pantoprazole have been received. A spontaneous report of a suicide involving an overdosage of pantoprazole (560 mg) has been received; however, the death was more reasonably attributed to the unknown doses of chloroquine and zopiclone which were also taken since two other reported cases of pantoprazole overdosage involved similar amounts of pantoprazole (400 and 600 mg) with no adverse effects observed. One patient in a flexible dosing study of refractory peptic ulcer disease received a dose of 320 mg per day for 3 months; treatment was well tolerated. Doses of up to 240 mg per day, given intravenously for seven days, have been administered to healthy subjects and have been well tolerated.

Pantoprazole is not removed by hemodialysis.

Single oral doses of pantoprazole at 709 mg/kg, 798 mg/kg and 887 mg/kg were lethal to mice, rats and dogs, respectively. The symptoms of acute toxicity were hypoactivity, ataxia, hunched sitting, limb-splay, lateral position, segregation, absence of ear reflex, and tremor.

DOSAGE AND ADMINISTRATION

Treatment of Erosive Esophagitis

The recommended adult oral dose is 40 mg given once daily for up to 8 weeks. For those patients who have not healed after 8 weeks of treatment, an additional 8-week course of PROTONIX may be considered. (See INDICATIONS AND USAGE)

No dosage adjustment is necessary in patients with mild, moderate or severe renal insufficiency or in elderly patients. No dosage adjustment is necessary in patients undergoing hemodialysis. No dosage adjustment is needed in patients with mild or moderate hepatic impairment. The pharmacokinetics of pantoprazole have not yet been well characterized in patients with severe hepatic impairment. Therefore, the potential for modest drug accumulation (≤ 21%) when dosed once daily needs to be weighed against the potential for reduced acid control when dosed every other day in these patients.

PROTONIX Delayed-Release Tablets should be swallowed whole, with or without food in the stomach. Concomitant administration of antacids does not affect the absorption of PROTONIX.

Patients should be cautioned that PROTONIX Delayed-Release Tablets should not be split, chewed or crushed.

HOW SUPPLIED

PROTONIX is supplied as 40 mg yellow oval biconvex delayed-release tablets imprinted with PROTONIX (brown ink) on one side.

They are available as follows:

NDC 0008-0841-81 bottles of 90

Storage

Store PROTONIX Delayed-Release Tablets at 20°–25°C (68°–77°F); excursion permitted to 15°-30°C (59°-86°F). [See USP Controlled Room Temperature].

Rx only

US Patent No. 4,758,579

Manufactured for Wyeth Laboratories
A Wyeth-Ayerst Company
Philadelphia, PA 19101
under license from
Byk Gulden Pharmaceuticals
D78467 Konstanz, Germany

United States Patent [19]

Kohl et al.

[11] **Patent Number: 4,758,579**

[45] **Date of Patent: Jul. 19, 1988**

[54] **FLUOROALKOXY SUBSTITUTED BENZIMIDAZOLES USEFUL AS GASTRIC ACID SECRETION INHIBITORS**

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[73] Assignee: **BYK Gulden Lomberg Chemische Fabrik GmbH**, Konstanz, Fed. Rep. of Germany

[21] Appl. No.: **45,799**

[22] Filed: **Apr. 28, 1987**

Related U.S. Application Data

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[30] **Foreign Application Priority Data**

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Jun. 16, 1984 [CH] Switzerland 2901/84

[51] **Int. Cl.**[4] **C07D 403/12**; A61K 31/44
[52] **U.S. Cl.** **514/338**; 546/271
[58] **Field of Search** 546/271; 514/338

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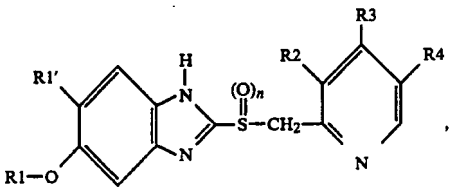
Primary Examiner—Jane T. Fan
Attorney, Agent, or Firm—Berman, Aisenberg & Platt

[57] **ABSTRACT**

Dialkoxypyridines of formula I



(I)

wherein

R1 is 1–3C-alkyl which is completely or predominantly substituted by fluorine, or a chlorodifluoromethyl radical and

R1' is hydrogen, halo, trifluoromethyl, 1–3C-alkyl, or 1–3C-alkoxy which is optionally completely or predominantly substituted by fluorine, or

R1 and R1', together with the oxygen atom to which R1 is bonded, are 1–2C-alkylenedioxy, which is optionally completely or partly substituted by fluorine, or chlorotrifluoroethylenedioxy,

R3 is 1–3C-alkoxy,

one of R2 and R4 is 1–3C-alkoxy and the other is a hydrogen atom or 1–3C-alkyl and

n is 0 or 1,

and salts thereof are new compounds with a pronounced protective action on the stomach. Processes for preparing these compounds, medicaments containing them and their use, as well as intermediate compounds and their use for preparing the subject dialkoxypyridines, are disclosed.

28 Claims, No Drawings

FLUOROALKOXY SUBSTITUTED BENZIMIDAZOLES USEFUL AS GASTRIC ACID SECRETION INHIBITORS

This application is a continuation of Ser. No. 748,591, filed June 14, 1985 now abandoned.

RELATED APPLICATIONS

The disclosed and claimed subject matter is related to that of applications Ser. No. 606,872 (filed May 1, 1984), Ser. No. 606,873 (filed May 1, 1984) and Ser. No. 794,230 (filed Oct. 29, 1985) now abandoned.

FIELD OF THE INVENTION

The invention relates to new dialkoxypyridines, processes for their preparation, their use and medicaments containing them. The compounds according to the invention are used in the pharmaceutical industry as intermediates and for the preparation of medicaments.

BACKGROUND

European Patent Application No. 0,005,129 concerns substituted pyridylsulfinylbenzimidazoles which are said to have properties of inhibiting secretion of gastric acid. The use of a number of benzimidazole derivatives for inhibiting secretion of gastric acid is referred to in European Patent Application No. 0,074,341. British Patent Application GB No. 2,082,580 involves tricyclic imidazole derivatives which are said to inhibit secretion of gastric acid and to prevent ulcer formation. In U.S. Pat. No. 4,472,409 and in U.S. applications Ser. No. 606,872 and Ser. No. 606,873 (both filed on May 1, 1984) trifluoromethyl compounds, fluoroalkoxy compounds and tricyclic ethers with benzimidazole structure and a marked protective effect on the stomach are described.

SUMMARY OF THE INVENTION

It has now been found, surprisingly, that the dialkoxypyridines of the present invention have interesting and unexpected properties which advantageously distinguish them from known compounds.

The invention relates to dialkoxypyridines of formula I and salts thereof, to medicament compositions having (as an active ingredient thereof) an effective amount of a compound of formula I or of a pharmaceutically-acceptable salt thereof, to the use of these compounds and compositions to inhibit gastric acid secretion in and to protect the stomach and intestines of warm-blooded animals, to the formulation of the medicament compositions, to the synthesis of dialkoxypyridines of formula I and of salts thereof, to compounds of formula III and to their use in preparing compounds of formula I and salts of the latter.

An object of this invention is to provide compounds and compositions useful for inhibiting gastric acid secretion in warm-blooded animals.

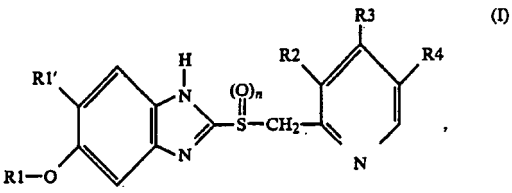
Another object is to provide compounds and compositions which protect the stomach and intestines of warm-blooded animals.

A further object is to provide chemically-stable compounds and compositions which have a wide therapeutic range and lack substantial side effects and especially to impart higher chemical stability to pyridylsulfinylbenzimidazoles.

Still further objects are apparent from the following description.

DETAILS

The invention relates to new dialkoxypyridines of formula I:



(I)

wherein

R1 represents a 1–3C-alkyl radical which is completely or predominantly substituted by fluorine, or a chlorodifluoromethyl radical and

R1' represents hydrogen (—H), halo, trifluoromethyl, a 1–3C-alkyl radical, or a 1–3C-alkoxy radical which is, optionally, completely or predominantly substituted by fluorine, or

R1 and R1' together, with inclusion of the oxygen atom to which R1 is bonded, represent a 1–2C-alkylenedioxy radical which is, optionally, completely or partly substituted by fluorine, or a chlorotrifluoroethylenedioxy radical,

R3 represents a 1–3C-alkoxy radical,

one of the radicals R2 and R4 represents a 1–3C-alkoxy radical and the other represents a hydrogen atom (—H) or a 1–3C-alkyl radical and

n represents the number 0 or 1,

and to salts of these compounds.

Examples of 1–3C-alkyl radicals which are completely or predominantly substituted by fluorine are the 1,1,2-trifluoroethyl radical, the perfluoropropyl radical, the perfluoroethyl radical, and in particular, the 1,1,2,2-tetrafluoroethyl radical, the trifluoromethyl radical, the 2,2,2-trifluoroethyl radical and the difluoromethyl radical.

Halogen in the context of the present invention is bromine, chlorine and, in particular, fluorine.

1–3C-alkyl radicals are the propyl, isopropyl, ethyl and, in particular, methyl radical.

1–3C-alkoxy radicals contain, in addition to the oxygen atom, the mentioned 1–3C-alkyl radicals. The methoxy radical is preferred.

1–3C-Alkoxy radicals which are completely or predominantly substituted by fluorine contain, in addition to the oxygen atom, the mentioned 1–3C-alkyl radicals which are completely or predominantly substituted by fluorine. Examples include the 1,1,2,2-tetrafluoroethoxy, the trifluoromethoxy, the 2,2,2-trifluoroethoxy and the difluoromethoxy radicals.

Examples of 1–2C-alkylenedioxy radicals which are, optionally, completely or partly substituted by fluorine are the 1,1-difluoroethylenedioxy radical (—O—CF_2—CH_2—O—), the 1,1,2,2L-tetrafluoroethylenedioxy radical (—O—CF_2—CF_2—O—), the 1,1,2-trifluoroethylenedioxy radical (—O—CF_2—CHF—O—) and, in particular, the difluoromethylenedioxy radical (—O—CF_2—O—), as substituted radicals, and the ethylenedioxy radical and the methylenedioxy radical, as unsubstituted radicals.

Preferred salts of compounds of the formula I in which n denotes the number 0 (sulfides) are all the acid-addition salts. The pharmacologically-acceptable salts of inorganic and organic acids usually employed in

galenics are notable examples. Pharmacologically-unacceptable salts which may be obtained initially via industrial-scale processes are converted into pharmacologically-acceptable salts by conventional processes. Examples of suitable pharmacologically-acceptable salts are water-soluble and water-insoluble acid-addition salts, such as the hydrochloride, hydrobromide, hydriodide, phosphate, nitrate, sulfate, acetate, citrate, gluconate, benzoate, hibenzate, fendizoate, butyrate, sulfosalicylate, maleate, laurate, malate, fumarate, succinate, oxalate, tartrate, amsonate, embonate, metembonate, stearate, tosylate, 2-hydroxy-3-naphthoate, 3-hydroxy-2-naphthoate and mesylate.

Preferred salts of compounds of formula I in which n denotes 1 (sulfoxides) are basic salts, in particular pharmacologically-acceptable salts with inorganic and organic bases usually employed in pharmacy. Examples of pharmacologically-acceptable basic salts are the sodium, potassium, calcium and aluminum salts.

One embodiment (embodiment a) of the invention comprises compounds of formula I wherein R1' represents hydrogen (—H), and R1, R2, R3, R4 and n have the previously-noted meanings; and their salts.

Another embodiment (embodiment b) of the invention comprises compounds of formula I wherein R1' represents halogen, trifluoromethyl, a 1–3C-alkyl radical or a 1–3C-alkoxy radical which is, optionally, completely or predominantly substituted by fluorine; and R1, R2, R3, R4 and n have the previously-mentioned meanings; and their salts.

Another embodiment (embodiment c) of the invention comprises compounds of formula I wherein R1 and R1' together, including the oxygen atom to which R1 is bonded, comprise a 1–2C-alkylenedioxy radical, and R2, R3, R4 and n have the aforementioned meanings; and their salts.

Another embodiment (embodiment d) of the invention comprises compounds of formula I wherein R1 and R1' together, including the oxygen atom to which R1 is bonded, comprise a 1–2C-alkylenedioxyradical which is completely or partly substituted by fluorine, and R2, R3, R4 and n have the previously-noted meanings; and their salts.

Another embodiment (embodiment e) of the invention comprises compounds of formula I wherein R1 and R1' together, including the oxygen atom to which R1 is bonded, comprise a chlorotrifluoroethylenedioxy radical, and R2, R3, R4 and n have their previously-ascribed meanings; and their salts.

Preferred compounds of embodiment a are those of formula I wherein R1 represents 1,1,2,2-tetrafluoroethyl, trifluoromethyl, 2,2,2-trifluoroethyl, difluoromethyl or chlorodifluoromethyl, R1' represents hydrogen, R3 represents methoxy, one of the radicals R2 and R4 represents methoxy and the other represents hydrogen or methyl, and n represents the number 0 or 1; and the salts of these compounds.

Preferred compounds of embodiment b are those of formula I wherein R1 represents difluoromethyl, R1' represents difluoromethoxy or methoxy, R3 represents methoxy, one of the radicals R2 and R4 represent methoxy and the other represents hydrogen or methyl, and n represents the number 0 or 1; and the salts of these compounds.

Preferred compounds of embodiment c are those of formula I wherein R1 and R1' together, combined with the oxygen atom to which R1 is bonded, represent a methylenedioxy or ethylenedioxy radical, R3 represents methoxy, one of the radicals R2 and R4 represents methoxy and the other represents hydrogen or methyl, and n represents the number 0 or 1; and the salts of these compounds.

Preferred compounds of embodiment d are those of formula I wherein R1 and R1' together, combined with the oxygen atom to which R1 is bonded, represent a difluoromethylenedioxy radical or a 1,1,2-trifluoroethylenedioxy radical, R3 represents methoxy, one of the radicals R2 and R4 represents methoxy and the other represents hydrogen or methyl, and n represents the number 0 or 1; and the salts of these compounds.

Preferred compounds of embodiment e are those of formula I wherein R1 and R1' together, including the oxygen atom to which R1 is bonded, represent a chlorotrifluoroethylenedioxy radical, R3 represents methoxy, one of the radicals R2 and R4 represents methoxy and the other represents hydrogen or methyl, and n represents 0 or 1; and the salts of these compounds.

Examples of compounds according to the invention are:

2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-5-trifluoromethoxy-1H-benzimidazole,
2-[(4,5-dimethoxy-3-methyl-2-pyridyl)-methylthio]-5-trifluoromethoxy-1H-benzimidazole,
2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole,
2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole,
2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-5-(2,2,2-trifluoroethoxy)-1H-benzimidazole,
2-[(4,5-dimethoxy-3-methyl-2-pyridyl)-methylthio]-5-(2,2,2-trifluoroethoxy)-1H-benzimidazole,
5-difluoromethoxy-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
5-difluoromethoxy-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-benzimidazole,
5-chlorodifluoromethoxy-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
5-chlorodifluoromethoxy-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-benzimidazole,
5,6-bis(difluoromethoxy)-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
5,6-bis(difluoromethoxy)-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-benzimidazole,
5-difluoromethoxy-6-methoxy-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
5-difluoromethoxy-6-methoxy-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)-methylthio]-1H-benzimidazole,
2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-5-trifluoromethoxy-1H-benzimidazole,
2-[(4,5-dimethoxy-2-pyridyl)methylthio]-5-trifluoromethoxy-1H-benzimidazole,
2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole,
2-[(4,5-dimethoxy-2-pyridyl)methylthio]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole,
2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-5-(2,2,2-trifluoroethoxy)-1H-benzimidazole,
2-[(4,5-dimethoxy-2-pyridyl)methylthio]-5-(2,2,2-trifluoroethoxy)-1H-benzimidazole,
5-difluoromethoxy-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
5-difluoromethoxy-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazole,
5-chlorodifluoromethoxy-2-[(4,5-dimethoxy-2-pyridyl)-methylsulfinyl]-1H-benzimidazole,

5-chlorodifluoromethoxy-2-[(4,5-dimethoxy-2-pyridyl)-methylthio]-1H-benzimidazole,
5,6-bis(difluoromethoxy)-2-[(4,5-dimethoxy-2-pyridyl)-methylsulfinyl]-1H-benzimidazole,
5,6-bis(difluoromethoxy)-2-[(4,5-dimethoxy-2-pyridyl)-methylthio]-1H-benzimidazole,
5-difluoromethoxy-6-methoxy-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
5-difluoromethoxy-6-methoxy-2-[4,5-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazole,
2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylsulfinyl]-5-trifluoromethoxy-1H-benzimidazole,
2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylthio]-5-trifluoromethoxy-1H-benzimidazole,
2,[(3,4-dimethoxy-5-methyl-2-pyridyl)methylsulfinyl]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole,
2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylthio]-5-(1,1,2,2-tetrafluoro-ethoxy)-1H-benzimidazole,
2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylsulfinyl]-5-(2,2,2-trifluoroethoxy)-1H-benzimidazole,
2-[(3,4-dimethoxy-5-methyl-2-pyridyl)-methylthio]-5-(2,2,2-trifluoroethoxy)-1H-benzimidazole,
5-difluoromethoxy-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
5-difluoromethoxy-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylthio]-1H-benzimidazole,
5-chlorodifluoromethoxy-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
5-chlorodifluoromethoxy-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylthio]-1H-benzimidazole,
5,6-bis(difluoromethoxy)-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
5,6-bis(difluoromethoxy)-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylthio]-1H-benzimidazole,
5-difluoromethoxy-6-methoxy-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
5-difluoromethoxy-6-methoxy-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylthio]-1H-benzimidazole,
2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-5-trifluoromethoxy-1H-benzimidazole,
2-[(3,4-dimethoxy-2-pyridyl)methylthio]-5-trifluoromethoxy-1H-benzimidazole,
2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole,
2-[(3,4-dimethoxy-2-pyridyl)methylthio]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole,
2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-5-(2,2,2-trifluoroethoxy)-1H-benzimidazole,
2-[(3,4-dimethoxy-2-pyridyl)methylthio]-5-(2,2,2-trifluoroethoxy)-1H-benzimidazole,
5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazole,
5-chlorodifluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)-methylsulfinyl]-1H-benzimidazole,
5-chlorodifluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)-methylthio]-1H-benzimidazole,
5,6-bis(difluoromethoxy)-2-[(3,4-dimethoxy-2-pyridyl)-methylsulfinyl]-1H-benzimidazole,
5,6-bis(difluoromethoxy)-2-[(3,4-dimethoxy-2-pyridyl)-methylthio]-1H-benzimidazole,
5-difluoromethoxy-6-methoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
5-difluoromethoxy-6-methoxy-2-[(3,4-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazole,
2,2-difluoro-6-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo-[4,5-f]benzimidazole,
2,2-difluoro-6-[(4,5-dimethoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo-[4,5-f]benzimidazole,
2,2-difluoro-6-[(3-methyl-4,5-dimethoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazole,
2,2-difluoro-6-[(3-methyl-4,5-dimethoxy-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazole,
6-[(4,5-diethoxy-3-methyl-2-pyridyl)methylthio]-2,2-difluoro-5H-[1,3]-dioxolo[4,5-f]benzimidazole,
6-[(4,5-diethoxy-3-methyl-2-pyridyl)methylsulfinyl]-2,2-difluoro-5H-[1,3]-dioxolo[4,5-f]benzimidazole,
6,6,7-trifluoro-6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio-1H-[1,4]-dioxino[2,3-f]benzimidazole,
6,6,7-trifluoro-6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazole,
6,6,7-trifluoro-6,7-dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-[1,4]-dioxino-[2,3-f]benzimidazole,
6,6,7-trifluoro-6,7-dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazole,
2-[(4,5-diethoxy-2-pyridyl)methylthio]6,6,7-trifluoro-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazole,
2-[(4,5-diethoxy-2-pyridyl)methylsulfinyl]-6,6,7-trifluoro-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazole,
2-[(4,5-diethoxy-3-methyl-2-pyridyl)methylthio]-6,6,7-trifluoro-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazole,
2-[(4,5-diethoxy-3-methyl-2-pyridyl)methylsulfinyl]-6,6,7-trifluoro-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazole,
6,6-difluoro-6,7-dihydro-2-[(4,5-dimethoxy-2-pyridyl)-methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazole,
6,6-difluoro-6,7-dihydro-2-[(4,5-dimethoxy-2-pyridyl)-methylsulfinyl]-1H-[1,4]-dioxinio[2,3-f]benzimidazole,
6,6-difluoro-6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazole,
6,6-difluoro-6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazole,
6,6,7,7-tetrafluoro-6,7-dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazole,
6,6,7,7-tetrafluoro-6,7-dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazole,
6,6,7,7-tetrafluoro-6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazole,
6,6,7,7-tetrafluoro-6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxine[2,3-f]benzimidazole,
6-chloro-6,7,7-trifluoro-6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-[1,4]dioxino[2,3-f]benzimidazole,
6-chloro-6,7,7-trifluoro-6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazole,
6-chloro-6,7,7-trifluoro-6,7-dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]-benzimidazole,
6-chloro-6,7,7-trifluoro-6,7-dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazole,

2,2-difluoro-6-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazole,
2,2-difluoro-6-[(3,4-dimethoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo-[4,5-f]benzimidazole,
2,2-difluoro-6-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazole,
2,2-difluoro-6-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazole,
6-[(3,4-diethoxy-5-methyl-2-pyridyl)methylthio]-2,2-difluoro-5H-[1,3]-dioxolo[4,5-f]benzimidazole,
6-[(3,4-diethoxy-5-methyl-2-pyridyl)methylsulfinyl]-2,2-difluoro-5H-[1,3]-dioxolo[4,5-f]benzimidazole,
6,6,7-trifluoro-6,7-dihydro-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazole,
6,6,7-trifluoro-6,7-dihydro-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazole,
6,6,7-trifluoro-6,7-dihydro-2-[(3,4-dimethoxy-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazole,
6,6,7-trifluoro-6,7-dihydro-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazole,
2-[(3,4-diethoxy-2-pyridyl)methylthio]-6,6,7-trifluoro-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazole,
2-[(3,4-diethoxy-2-pyridyl)methylsulfinyl]-6,6,7-trifluoro-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazole,
2-[(3,4-diethoxy-5-methyl-2-pyridyl)methylthio]-6,6,7-trifluoro-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazole,
2-[(3,4-diethoxy-5-methyl-2-pyridyl)methylsulfinyl]-6,6,7-trifluoro-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazole,
6,6-difluoro-6,7-dihydro-2-[(3,4-dimethoxy-2-pyridyl)-methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazole,
6,6-difluoro-6,7-dihydro-2-[(3,4-dimethoxy-2-pyridyl)-methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazole,
6,6-difluoro-6,7-dihydro-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazole,
6,6-difluoro-6,7-dihydro-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazole,
6,6,7,7-tetrafluoro-6,7-dihydro-2-[(3,4-dimethoxy-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazole,
6,6,7,7-tetrafluoro-6,7-dihydro-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazole,
6,6,7,7-tetrafluoro-6,7-dihydro-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazole,
6,6,7,7-tetrafluoro-6,7-dihydro-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazole,
6-chloro-6,7,7-trifluoro-6,7-dihydro-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benimidazole,
6-chloro-6,7,7-trifluoro-6,7-dihydro-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazole,
6-chloro-6,7,7-trifluoro-6,7-dihydro-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazole,
6-chloro-6,7,7-trifluoro-6,7-dihydro-2-[(3,4-dimethoxy-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazole,
6-[(4,5-dimethoxy-3-methyl-2-pyridyl)-methylthio]-5H-[1,3]dioxolo[4,5-f]benzimidazole,
6-[(4,5-dimethoxy-3-methyl-2-pyridyl)-methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazole,
6-[(4,5-dimethoxy-2-pyridyl)methylthio]-5H-[1,3]dioxolo[4,5-d]benzimidazole,
6-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazole,
6-[(3,4-dimethoxy-2-pyridyl)-methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazole,
6-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazole.
6-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]-benzimidazole,
6-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazole,
6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazole,
6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazole,
6,7-dihydro-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazole,
6,7-dihydro-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazole,
6,7-dihydro-2-[(3,4-dimethoxy-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazole and
6,7-dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazole,

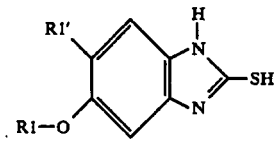
and salts of these compounds.

Due to the tautomerism in the imidazole ring, 5-substitution in the benzimidazole is identical to 6-substitution. Accordingly, in the compounds in which R1 and R1′ together, with inclusion of the oxygen atom to which R1 is bonded, represent a substituted ethylenedioxy radical, the 6-position in the [1,4]-dioxino[2,3-f]benzimidazole part is identical to the 7-position.

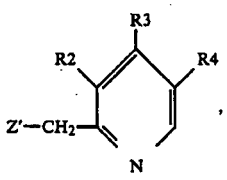
The invention furthermore relates to a process for the preparation of the dialkoxypyridines of formula I, wherein R1, R1′, R2, R3, R4 and n have their noted meanings, and of their salts.

The process comprises reacting:

(a) a mercaptobenzimidazole of formula II with a picoline derivative III

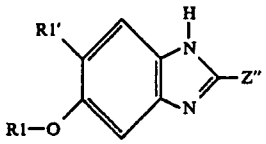


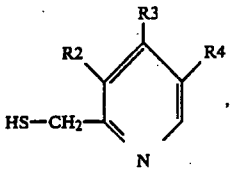
(II)



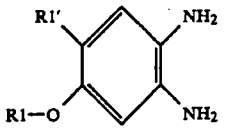
(III)

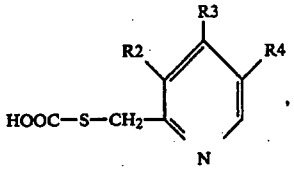
(b) a benzimidazole of formula IV with a mercaptopicoline V


(IV)

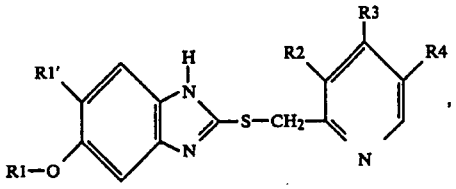

(V)

(c) an o-phenylenediamine of formula VI with a formic acid derivative VII


(VI)

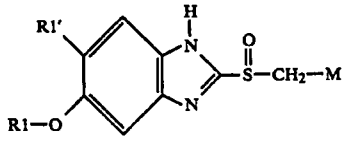

(VII)

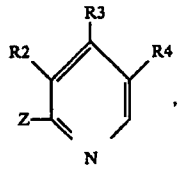
and, if appropriate, the 2-benzimidazolyl 2-pyridylmethyl sulfides of formula VIII obtained according to (a), (b) or (c)


(VIII)

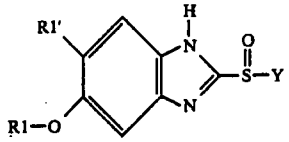
are then oxidized and/or converted into salts,

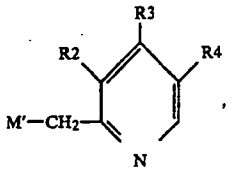
(d) a benzimidazole of formula IX with a pyridine derivative X


(IX)


(X)

(e) a sulfinyl compound of formula XI with a 2-picoline derivative XII


(XI)


(XII)

and, if appropriate, the products are converted into salts, Y, Z, Z' and Z'' being suitable leaving groups, M representing an alkali-metal atom (Li, Na or K), M' representing the equivalent of a metal atom and R1, R1', R2, R3, R4 and n having their above-mentioned meanings.

The compounds II–XII are employed in the indicated reactions in their free states or as salts.

Preparation processes (a), (b) and (c) lead to the sulfides according to the invention, and the oxidation of compounds VIII and processes (d) and (e) give sulfoxides according to the invention.

Those skilled in the art are familiar with suitable leaving groups Y, Z, Z' and Z''. A suitable leaving group Y is, for example, a group which forms a reactive sulfinic acid derivative together with the sulfinyl group to which it is bonded. Examples of suitable leaving groups Y are alkoxy, dialkylamino and alkylmercapto groups. Examples of suitable leaving groups Z, Z' or Z'' are halogen atoms, in particular chlorine atoms, or hydroxyl groups activated by esterification (for example with p-toluenesulfonic acid). The equivalent of a metal atom M' is, for example, an alkali-metal atom (Li, Na or K), or an alkaline-earth-metal atom (for example Mg), which is substituted by a halogen atom (for example Br, Grignard reagent), or any other optionally-substituted metal atom which is known to react like the noted metals in replacement reactions of organometallic compounds.

The reaction of II with III is carried out in known manner in suitable, preferably polar, protic or aprotic solvent (such as methanol, isopropanol, dimethyl sulfoxide, acetone, dimethylformamide or acetonitrile) with the addition of or exclusion of water. It is carried out, for example, in the presence of a proton acceptor. Examples of suitable proton acceptors are alkali-metal hydroxides, such as sodium hydroxide, alkali-metal carbonates, such as potassium carbonate, or tertiary amines, such as pyridine, triethylamine or ethyldiisopropylamine. Alternatively, the reaction is carried out without a proton acceptor, in which case, depending on the starting compounds, the acid-addition salts are first obtained in a particularly pure form. The reaction temperature is, e.g., between 0° and 150° C. (depending on the reactants involved), temperatures between 20° and 80° C. being preferred in the presence of proton acceptors and temperatures between 60° and 120° C. (in particular the boiling point of the solvent used) being preferred without proton acceptors. The reaction times are between 0.5 and 24 hours.

Reaction conditions similar to those in the reaction of II with III are used in the reaction of IV with V, which is carried out in a known manner.

The reaction of VI with VII is preferably carried out in polar, optionally water-containing solvents in the presence of a strong acid, for example hydrochloric acid, preferably at the boiling point of the solvent used.

The oxidation of the sulfides VIII is conventionally carried out under conditions known to be suitable for the oxidation of sulfides to sulfoxides [cf. J. Drabowicz and M. Mikolajczyk, *Organic Preparations and Procedures Int.* 14(1-2), 45–89 (1982) or E. Block in S. Patai, *The Chemistry of Functional Groups*, Supplement E, Part 1, pages 539–608, John Wiley and Sons (Interscience Publication), 1980]. Illustrative oxidizing agents are all reagents usually employed for the oxidation of sulfides to sulfoxides, for example hypohalites, and in particular peroxyacids, such as peroxyacetic acid, trifluoroperoxyacetic acid, 3,5-dinitroperoxybenzoic acid, peroxymaleic acid or, preferably, m-chloroperoxybenzoic acid.

The (oxidation) reaction temperature is between −70° C. and the boiling point of the solvent used (depending on the reactivity of the oxidizing agent and the degree of dilution), but preferably between −50° and +20° C. The oxidation is advantageously carried out in inert solvents, for example aromatic or chlorinated hydrocarbon, such as benzene, toluene, dichloromethane or chloroform; esters, such as ethyl acetate or isopropyl acetate; or ethers, such as dioxane, with the addition of water or without water.

The reaction of IX with X is preferably carried out in an inert solvent usually employed for the reaction of enolate ions with alkylating agents. Examples include aromatic solvents, such as benzene or toluene. The reaction temperature is as a rule between 0° and 120° C. (depending on the nature of the alkali-metal atom M and the leaving group Z), the boiling point of the solvent used being preferred. For example [if M represents Li (lithium) and Z represents Cl (chlorine) and the reaction is carried out in benzene], the boiling point of benzene (80° C.) is preferred.

The compounds XI are reacted with compounds XII in a conventional manner and under known conditions suitable for the reaction of organometallic compounds.

Depending on the nature of the starting compounds, which can optionally also be employed as salts, and depending on the reaction conditions, the compounds according to the invention are initially obtained either as free compounds or in the form of salts.

The salts are obtained by dissolving the free compounds in a suitable solvent, for example in a chlorinated hydrocarbon, such as methylene chloride or chloroform, a low molecular weight aliphatic alcohol (ethanol or isopropanol), an ether (diisopropyl ether), a ketone (acetone) or water, which contains the desired acid or base, or to which the desired acid or base is added (if necessary) in the precisely calculated stoichiometric amount.

The salts are obtained by filtration, reprecipitation, or precipitation or by evaporation of the solvent.

Resulting salts are converted into the free compounds by treatment with bases or acids, for example with aqueous sodium bicarbonate or with dilute hydrochloric acid, and the free compounds are optionally converted into their salts. In this manner, the compounds are purified, or pharmacologically-unacceptable salts are converted into pharmacologically-acceptable salts.

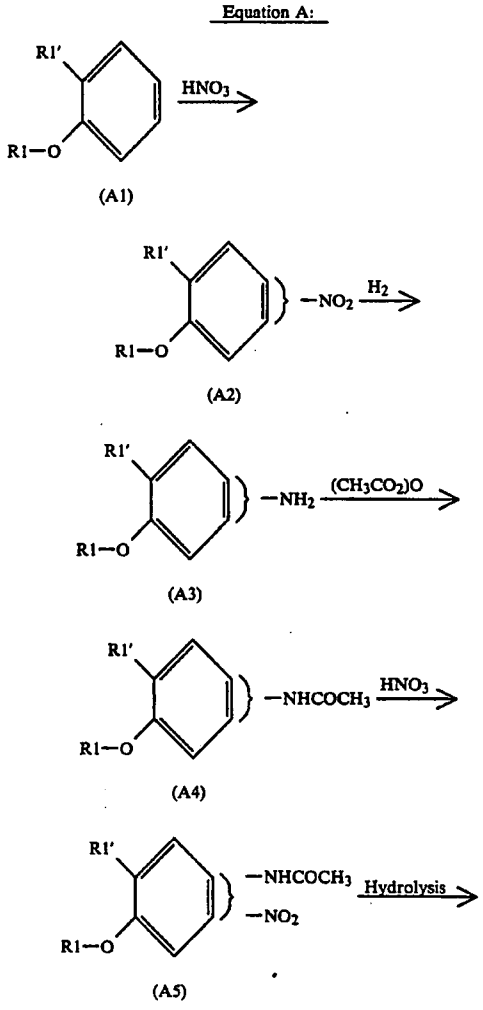
The sulfoxides according to the invention are optically active compounds. The invention therefore relates both to the enantiomers and to their mixtures and racemates. The enantiomers are separated by known methods (for example, by preparation and separation of corresponding diastereoisomers). However, the enantiomers are also prepared by asymmetric synthesis, for example by reaction of optically-active pure or diastereoisomerically pure compounds XI with compounds XII [cf. K. K. Andersen, *Tetrahedron Lett.*, 93 (1962)].

The compounds according to the invention are preferably synthesized by reaction of II with III and, if appropriate, subsequent oxidation of the sulfide VIII formed.

The compounds of the formula II are known (cf. German Offenlegungsschrift No. 3,132,613) and are prepared by known methods from known starting materials. Compounds II are obtained, for example, by reacting compounds VI with carbon disulfide in the presence of alkali-metal hydroxides or with alkali-metal O-ethyl dithiocarbonates.

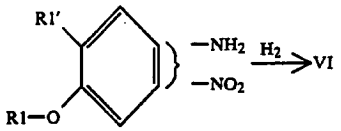
Compounds of formula VI are synthesized in a known manner by the general preparation methods described in the following equation A:

Equation A:



-continued

Equation A:



(A6)

The starting compounds A1–A3 are prepared by known methods or by methods analogous to the following: [cf. *J. Org. Chem.* 44, 2907–2910 (1979); *J. Org. Chem.* 29, 1–11 (1964); German Offenlegungsschrift No. 2,029,556; German Offenlegungsschrift No. 2,848,531; *J. Fluorine Chem.* 18, 281–91 (1981); and *Synthesis* 1980, 727–8]. Optionally, isomer mixtures are prepared in the case of non-identical substituents R1' and R1-0-.

Compounds IV, IX and XI are conventionally prepared, for example, from compounds II.

Compounds IX are obtained, for example, from compounds II by methylation, oxidation and subsequent deprotonation, for example, with alkali-metal hydrides or alcoholates or customary organometallic compounds. Compounds X are prepared according to Z. Talik, *Roczniki chem.* 35, 475 (1961).

Compounds III are prepared in various ways:

1. Compounds III where R2 and R3=1–3C-alkoxy and R4=hydrogen or 1–3C-alkyl.

These compounds are prepared, for example, starting from 3-hydroxy- or 3-hydroxy-5-alkyl-pyridines (which are known or are conventionally prepared from known starting materials) by benzylation of the hydroxyl group (for example with potassium hydroxide and benzyl chloride in dimethyl sulfoxide), N-oxidation (for example with 30% strength hydrogen peroxide), nitration in the 4-position (for example with nitrating acid), replacement of the nitro group by the 1–3C-alkoxy group (for example by reaction with alkali-metal alkoxide), reductive debenzylation and simultaneous N-deoxygenation (for example with hydrogen over palladium-on-charcoal in an acid medium), introduction of the hydroxymethyl group in the o-position relative to the pyridine nitrogen (for example by reaction with alkaline formalin solution), conversion of the 3-hydroxy group into a 1–3C-alkoxy group (for example by alkylation with 1–3C-alkyl iodide in a basic medium) and introduction of the leaving group Z' (for example by reaction with thionyl chloride). In a preferred alternative, the compounds are prepared starting from 3-hydroxy-2-alkyl- or 3-hydroxy-2,5-dialkyl-pyridines (which are known or are conventionally prepared) by alkylation of the hydroxyl group (for example with potassium hydroxide and methyl iodide in dimethyl sulfoxide), N-oxidation (for example with 30% strength hydrogen peroxide), nitration in the 4-position (for example with nitric acid), replacement of the nitro group by the 1–3C-alkoxy group (for example by reaction with alkali-metal alkoxide), conversion into the 2-acetoxymethylpyridine (for example with hot acetic anhydride), hydrolysis (for example with dilute sodium hydroxide solution) to the hydroxymethyl group and introduction of the leaving group Z' (for example by reaction with thionyl chloride).

2. Compounds III where R3 and R4=1–3C-alkoxy and R2=hydrogen.

These compounds are prepared, for example, starting from known 5-hydroxy-2-methylpyridines by alkylation of the hydroxyl group (for example with 1–3C-alkyl iodide and potassium hydroxide in dimethyl sulfoxide), N-oxidation (for example with 30% strength hydrogen peroxide), nitration in the 4-position (for example with nitrating acid), replacement of the nitro group by the 1–3C-alkoxy group (for example by reaction with alkali metal alkoxide), conversion into the 2-acetoxymethylpyridine (for example with hot acetic anhydride), hydrolysis (for example with dilute sodium hydroxide solution) to the 2-hydroxymethyl group and introduction of the leaving group Z' (for example by reaction with thionyl chloride).

3. Compounds III where R3 and R4=1–3C-alkoxy and R2=1–3C-alkyl.

These compounds are prepared, for example, starting from 2-methyl-3-alkyl-4-alkoxypyridines which are known or are conventionally prepared (see, for example, European Pat. No. A-0,080,602), by N-oxidation (for example with 30% strength hydrogen peroxide), controlled acetoxylation and subsequent hydrolysis in the 5-position (for example with acetic anhydride and subsequently sodium hydroxide solution), alkylation of the 5-hydroxy group (for example with 1–3C-alkyl iodide and sodium hydroxide solution in dimethyl sulfoxide), N-oxidation (for example with m-chloroperoxybenzoic acid), conversion into the 2-acetoxymethylpyridine (for example with hot acetic anhydride), hydrolysis (for example with dilute sodium hydroxide solution) to the 2-hydroxymethyl group and introduction of the leaving group Z' (for example by reaction with thionyl chloride).

The specific reaction conditions (temperatures, reaction times, solvents and the like) in the synthesis routes outlined above for the preparation of the compounds III are familiar to the artisan. The preparation of individual representatives of the compounds III is described in the examples. Other representatives are prepared analogously.

The compounds III, wherein R3 represents 1–3C-alkoxy, one of the radicals R2 and R4 represents a 1–3C-alkoxy radical and the other represents a 1–3C-alkyl radical are new and are also the subject of the invention.

The compounds V, VII and XII are prepared, for example, starting from the compounds III and by employing conventional routes.

The following examples illustrate the invention in more detail without limiting it. In the examples, m.p. denotes melting point, decomp. represents decomposition and b.p. represents boiling point.

EXAMPLES

1. 2-[(4,5-Dimethoxy-2-pyridyl)methylthio]-5-trifluoromethoxy-1H-benzimidazole

1.57 g of 2-chloromethyl-4,5-dimethoxypyridinium chloride are added to a solution of 1.64 g of 2-mercapto-5-trifluoromethoxy-1H-benzimidazole in 40 ml of ethanol and 20 ml of 1N sodium hydroxide solution, the mixture is stirred at 20° C. for 2 hours and then at 40° C. for a further hour, the ethanol is distilled off on a rotary evaporator (10 mbar/40° C.) and the colorless precipitate which thereby separates out is filtered off over a suction filter, rinsed with 1N sodium hydroxide solution and water and dried. 2.15 g (79% of theory) of the title compound of m.p. 92°–93° C. are obtained.

5-Chlorodifluoromethoxy-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazole, 5-difluoromethoxy-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazole (oil), 5,6-bis(difluoromethoxy)-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazole, . 5-difluoromethoxy-6-methoxy-2-[(4,5 dimethoxy-2-pyridyl)methylthio]-1H-benzimidazole (m.p. 159°–160° C.) and 5-difluoromethoxy-6-fluoro-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazole are obtained analogously by reacting 5-chlorodifluoromethoxy-2-mercapto-1H-benzimidazole, 5-difluoromethoxy-2-mercapto-1H-benzimidazole, 5,6-bis(difluoromethoxy)-2-mercapto-1H-benzimidazole, 5-difluoromethoxy-2-mercapto-6-methoxy-1H-benzimidazole and 5-difluoromethoxy-6-fluoro-2-mercapto-1H-benzimidazole with 2-chloromethyl-4,5-dimethoxypyridinium chloride.

2. 2-[(4,5-Dimethoxy-2-pyridyl)methylsulfinyl]-5-trifluoromethoxy-1H-benzimidazole

5.5 ml of a 0.2M solution of m-chloroperoxybenzoic acid in methylene chloride are added dropwise to a solution of 0.36 g of 2-[4,5-dimethoxy-2-pyridyl)methylthio]-5-trifluoromethoxy-1H-benzimidazole in 10 ml of methylene chloride at −50° C. and the mixture is stirred at the stated temperature for a further 30 minutes. After addition of 0.3 ml of triethylamine, the cold reaction mixture is stirred into 10 ml of 5% strength sodium thiosulfate solution and 10 ml of 5% strength sodium carbonate solution. After phase separation three further extrations with 10 ml of methylene chloride are performed, the combined organic phases are washed once with 5 ml of 5% strength sodium thiosulfate solution and dried. The drying agent (magnesium sulfate) is filtered off and the filtrate is concentrated. The residue is crystallized with diisopropyl ether and is then reprecipitated from methylene chloride/diisopropyl ether. 0.27 g (72% of theoretical) of the title compound is obtained as a colorless solid of m.p. 159°–61° C. (decomp.).

5-Chlorodifluoromethoxy-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole, 5-difluoromethoxy-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole [m.p. 159° C. (decomp.)], 5,6-bis(difluoromethoxy)-2-[(4,5-dimethoxy-2-pyridyl)-methylsulfinyl]-1H-benzimidazole, 5-difluoromethoxy-6-methoxy-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole and 5-difluoromethoxy-6-fluoro-2,2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole are obtained analogously by oxidation of other sulfides of Example 1 with m-chloroperoxybenzoic acid.

3. 2-[(4,5-Dimethoxy-2-pyridyl)methylthio]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole

1.40 g of the title compound are obtained as a yellow oil by the procedure described in Example 1, by reacting 1.07 g of 2-mercapto-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole with 0.90 g of 2-chloromethyl-4,5-dimethoxypyridinium chloride in 15 ml of ethanol with the addition of 17 ml of 0.5N sodium hydroxide solution. Recrystallization from petroleum ether yields 1.20 g (72% of theoretical) of the desired compound as colorless crystals of m.p. 125°–127° C.

4. 2-[(4,5-Dimethoxy-2-pyridyl)methylsulfinyl]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole

A solution of the product in methylene chloride is obtained by the procedure described in Example 2 by oxidation of 0.76 g of 2-[(4,5-dimethoxy-2-pyridyl)methylthio]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole with 19 ml of a 0.1M solution of m-chloroperoxybenzoic acid in 30 ml of methylene chloride at −40° C., after extraction. After drying the solution over magnesium sulfate, the drying agent is filtered off, the filtrate is concentrated and the residue is crystallized from methylene chloride/diisopropyl ether. 0.64 g (82% of theory) of the title compound is obtained in the form of colorless crystals of m.p. 160°–162° C. (decomp.).

5. 2-[(4,5-Dimethoxy-2-pyridyl)methylthio]-5-(2,2,2-trifluoroethoxy)-1H-benzimidazole

1.0 g of 2-mercapto-5-(2,2,2-trifluoroethoxy)-1H-benzimidazole is dissolved in 15 ml of ethanol and 8.5 ml of 1N sodium hydroxide solution, 0.90 g of 2-chloromethyl-4,5-dimethoxypyridinium chloride are added and the mixture is stirred for 20 hours. After addition of 30 ml of water, the mixture is extracted three times with 30 ml of methylene chloride each time, the methylene chloride phase is washed once with 5 ml of 0.1N sodium hydroxide solution, the combined organic phases are dried over magnesium sulfate and, after the drying agent has been filtered off, the filtrate is completely concentrated. 1.51 g (94% of theory) of the title compound are obtained as an amorphous solid residue of m.p. 55°–57° C.

6. 2-[(4,5-Dimethoxy-2-pyridyl)methylsulfinyl]-5-(2,2,2-trifluoroethoxy)-1H-benzimidazole

0.8 g of 2-[(4,5-dimethoxy-2-pyridyl)methylthio]-5-(2,2,2-trifluoroethoxy)-1H-benzimidazole is dissolved in 15 ml of dioxane and 2.5 ml of 1N sodium hydroxide solution. A mixture of 3 ml of 8% strength sodium hypochlorite solution and 3.5 ml of 1N sodium hydroxide solution are added dropwise in the course of 2 hours, while cooling to 0°–5° C. After addition of 5 ml of 5% strength sodium thiosulfate solution, the mixture is concentrated to dryness, the residue is taken up in water and the mixture is brought to pH 7 with phosphate buffer. The solid which has precipitated out is filtered off with suction, dried and recrystallized from ethyl acetate/diisopropyl ether. 0.45 g (55% of theory) of the title compound is obtained as colorless crystals of m.p. 142°–143° C. (decomp.).

7. 2-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylthio]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole

1.46 g (83% of theory) of the title compound of m.p. 127°–128° C. (colorless powder) are obtained by the procedure described in Example 1 by reaction of 1.07 g of 2-mercapto-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole with 0.96 g of 2-chloromethyl-4,5-dimethoxy-3-methylpyridinium chloride in 12 ml of ethanol, with the addition of 17 ml of 0.5N sodium hydroxide solution.

8. 2-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole

0.8 g of a pale yellow oil is obtained by the procedure described in Example 2 by oxidation of 0.99 g of 2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole with 12 ml of a 0.2M solution of m-chloroperoxybenzoic acid in methylene chloride at −40° C. for a reaction time of 1.5 hours. Recrystallization twice from methylene chloride/diisopropyl ether gives 0.30 g (34% of theory) of the title compound in the form of colorless crystals of m.p. 125° C. (decomp.).

9. 5-Difluoromethoxy-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-benzimidazole

0.64 g (84% of theory) of the title compound of m.p. 100°–102° C. (colorless crystalline powder) is obtained by the procedure described in Example 'by reaction of 0.38 g (2 mmol) of 5-difluoromethoxy-2-mercapto-1H-

benzimidazole with 0.48 g (2 mmol) of 2-chloromethyl-4,5-dimethoxy-3-methylpyridinium chloride in 10 ml of ethanol, with the addition of 8.8 ml of 1N sodium hydroxide solution, after two hours at 50° C.

10. 2-[(3,4-Dimethoxy-2-pyridyl)methylthio]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole

0.38 g (1.7 mmol) of 2-chloromethyl-3,4-dimethoxypyridinium chloride is added to a solution of 0.46 g (1.7 mmol) of 2-mercapto-5-(1,1,2,2-tetra fluoroethoxy)-1H-benzimidazole in 10 ml of ethanol, 10 ml of water and 1.8 ml of 2N sodium hydroxide solution; after the mixture has been stirred at 20° C. for one hour, a further 10 ml of water are added dropwise. The mixture is then stirred at 20° C. for a further four hours. The solid which has precipitated out is filtered off, washed with 0.01N sodium hydroxide solution and then with water until neutral and dried to constant weight. 0.63 g (90% of theory) of the title compound is obtained as a colorless crystalline powder of m.p. 98°–102° C.

5-Difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinylmethylthio)]-1H-benzimidazole (m.p. 104°–108° C.) and 5-difluoromethoxy-6-methoxy-2-[(3,4-dimethoxy-2-pyridylmethylthio)]-1H-benzimidazole (m.p. 137°–138° C.) are obtained analogously by reacting 5-difluoromethoxy-2-mercapto-1H-benzimidazole and 5-difluoromethoxy-6-methoxy-2-mercapto-1H-benzimidazole with 2-chloromethyl-3,4-dimethoxypyridinium chloride.

11. 2-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylthio]-5-trifluoromethoxy-1H-benzimidazole

1.40 g (70% of theory) of the title compound are obtained by the procedure described in Example 1 by reaction of 1.15 g of 2-mercapto-5-trifluoromethoxy-1H-benzimidazole with 1.20 g of 2-chloromethyl-4,5-dimethoxy-3-methylpyridinium chloride in 20 ml of isopropanol, with the addition of 20.5 ml of 0.5N sodium hydroxide solution. Recrystallization from diisopropyl ether/petroleum ether gives a product of m.p. 94°–97° C.

2-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylthio]-5-(2,2,2-trifluoro ethoxy)-1H-benzimidazole, 5-chlorodifluoromethoxy-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)-methylthio]-1H-benzimidazole, 5,6-bis(difluoromethoxy)-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-benzimidazole, 5-difluoromethoxy-6-methoxy-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-benzimidazole and 5-difluoromethoxy-6-fluoro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-benzimidazole are obtained analogously by reacting 2-mercapto-5-(2,2,2-trifluoroethoxy-1H-benzimidazole, 5-chlorodifluoromethoxy-2-mercapto-1H-benzimidazole, 5,6-bis(difluoromethoxy)-2-mercapto-1H-benzimidazole, 5-difluoromethoxy-2-mercapto-6-methoxy-1H-benzimidazole and 5-difluoromethoxy-6-fluoro-2-mercapto-1H-benzimidazole, respectively, with 2-chloromethyl-4,5-dimethoxy-3-methylpyridinium chloride.

12. 2-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-5-trifluoromethoxy-1H-benzimidazole

0.19 g (76% of theory) of the title compound is obtained as a colorless powder (158°–159° C. decomp.) by the procedure described in Example 2 by oxidation of 0.24 g of 2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-5-trifluoromethoxy-1H-benzimidazole with 3.3 ml of a 0.2M solution of m-chloroperoxybenzoic acid in methylene chloride at −50° C. and reprecipitation from methylene chloride/diisopropyl ether.

2-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-5-(2,2,2-trifluoroethoxy)-1H-benzimidazole, 5-chlorodifluoromethoxy-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazole, 5-difluoromethoxy-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazole [m.p. 133°–135° C. (decomp.)], 5,6-bis(difluoromethoxy)-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazole, 5-difluoromethoxy-6-methoxy-2-[4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazole, 5-difluoromethoxy-6-fluoro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazole and 2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole [m.p. 117°–119° C. (decomp.)] and 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole [m.p. 136° C. (decomp.)] are obtained analogously by oxidation of the sulfides of Examples 9 to 11 with m-chloroperoxybenzoic acid.

13. 2,2-Difluoro-6-[(4,5-dimethoxy-3-methyl-2-pyridyl)-methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazole

0.96 g of 2-chloromethyl-4,5-dimethoxy-3-methylpyridinium chloride are added to a solution of 0.92 g of 2,2-difluoro-5H-[1,3]-dioxolo[4,5-f]benzimidazole-6-thiol in 10 ml of ethanol and 10 ml of 1N sodium hydroxide solution. The yellow reaction mixture is stirred at 20° C. for 1 hour, a further 10 ml of water are added, whereupon a colorless solid precipitates out, the mixture is stirred for a further 5 hours and filtered and the residue is rinsed with 1N sodium hydroxide solution and water and dried to constant weight. The amorphous powder is recrystallized from methylene chloride/-diisopropyl ether. 1.5 g (93% of theory) of the title compound are obtained in the form of colorless crystals of m.p. 160°–161° C.

6,6,7-Trifluoro-6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-[1,4]dioxino[2,3-f]benzimidazole, 6-chloro-6,7,7-trifluoro-6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazole and 6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]-benzimidazole are obtained analogously by reacting 6,6,7-trifluoro-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazole-2-thiol, 6-chloro-6,7,7-trifluoro-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazole-2-thiol or 6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazole-2-thiol, respectively, with 2-chloromethyl-4,5-dimethoxy-3-methylpyridinium chloride.

14. 2,2-Difluoro-6-[(4,5-dimethoxy-3-methyl-2-pyridyl)-methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazole

21 ml of a 0.1N solution of m-chloroperoxybenzoic acid in methylene chloride are added dropwise to a suspension, cooled to −40° C., of 0.80 g of 2,2-difluoro-6[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]-benzimidazole in 10 ml of methylene chloride in the course of 10 minutes. The mixture is stirred for a further 20 minutes, during which the temperature is allowed to rise to −20° C., and 0.5 ml of triethylamine are added and the reaction mixture is poured into 40 ml of 5% strength sodium thiosulfate solution and 5% strength sodium carbonate solution. After phase separation, the aqueous phase is extracted twice more with 20 ml of methylene chloride each time; the combined organic phases are washed with a mixture of 5 ml of sodium thiosulfate solution and 5 ml of sodium carbonate solution, dried and concentrated. The residue is recrystallized from methylene chloride/diisopropyl ether. 0.62 g (75% of theory) of the title compound is obtained; decomp. 189°–190° C.

6,6,7-Trifluoro-6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazole, 6-chloro-6,7,7-trifluoro-6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazole and 6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazole are obtained analogously by oxidation of the other sulfides mentioned under Example 13 with m-chloroperoxybenzoic acid.

15. 6-[(4,5-Dimethoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazole

A brownish solid is obtained by the procedure described in Example 13 by reaction of 0.85 g of 5H-[1,3]-dioxolo[4,5-f]-benzimidazole-6-thiol with 0.98 g of 2-chloromethyl-4,5-dimethoxypyridinium chloride in 10 ml of ethanol and 10 ml of water, with the addition of 8.5 ml of 1N sodium hydroxide solution, after a reaction time of 20 hours and after concentration, by removing the solvent in vacuo, to a volume of 10 ml. The crude product is dissolved in 30 ml of methylene chloride, the solution is clarified with fuller's earth (for example, Tonsil ®), and concentrated. The residue is crystallized by addition of diisopropyl ether and the now pale yellow solid is boiled up in 5 ml of methanol. 0.90 g (60% of theory) of the title compound is obtained as a colorless solid of m.p. 198°–200° C.

16. 6-[(4,5-Dimethoxy-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]-benzimidazole

0.27 g of the title compound in the form of colorless crystals of m.p. 199° C. (decomp.) is obtained by the procedure described in Example 14 by oxidation of 0.7 g of 6-[(4,5-dimethoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]-benzimidazole with 23 ml of a 0.1M solution of m-chloroperoxybenzoic acid, after recrystallization from diethyl ether.

17. 2,2-Difluoro-6-[(3,4-dimethoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazole

1.05 g (92% of theory) of the title compound are obtained as a finely crystalline, colorless powder of m.p. 185°–187° C. by the procedure described in Example 13 by reaction of 0.69 g (3 mmol) of 2,2-difluoro-5H-[1,3]dioxolo[4,5-f]benzimidazole-6-thiol with 0.67 g (3 mmol) of 2-chloromethyl-3,4-dimethoxypyridinium chloride in a mixture of 10 ml of ethanol and 10 ml of water, with the addition of 3.3 ml of 2N sodium hydroxide solution, after a reaction time of 10 hours.

6-[(3,4-Dimethoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazole (m.p. 155°–157° C.) is obtained analogously by reacting 5H-[1,3]-dioxolo[4,5-f]benzimidazole-6-thiol with 2-chloromethyl-3,4-dimethoxypyridinium chloride.

18. 6-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazole

0.78 g (4 mmol) of 5H-[1,3]-dioxolo[4,5-f]benzimidazole-6-thiol is heated at the boiling point under reflux with 0.95 g (4 mmol) of 2-chloromethyl-4,5-dimethoxy-3-methylpyridinium chloride in 30 ml of isopropanol for 15 hours. The solid which has precipitated out is filtered off and extracted by stirring with isopropanol, the mixture is filtered again and the residue is dried to constant weight. 1.0 g (59% of theory) of the dihydrochloride of the title compound is obtained as a colorless solid of m.p. 206° C. (decomp.).

19. 2,2-Difluoro-6-[(4,5-dimethoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazole

6.3 ml of 1N sodium hydroxide solution are added dropwise to a solution, warmed to 50° C., of 0.69 g of 2,2-difluoro-5H-[1,3]-dioxolo[4,5-f]benzimidazole-6-thiol and 0.67 g of 2-chloromethyl-4,5-dimethoxypyridinium chloride in 9 ml of ethanol and 4 ml of water in the course of one minute. On cooling the clear reaction mixture to 20° C., a colorless precipitate separates out after a short time. The mixture is stirred at 20° C. for a further 5 hours and the precipitate is filtered off with suction over a suction filter, rinsed with 1N sodium hydroxide solution and water and dried to constant weight. The beige solid is dissolved in 10 ml of methylene chloride, insoluble constituents are filtered off, the filtrate is concentrated and the residue is made to crystallize by addition of diisopropyl ether after cooling. 1.02 g (90% of theory) of the title compound of m.p. 189°–191° C. are obtained.

6,6,7-Trifluoro-6,7-dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazole, 6-chloro-6,7,7-trifluoro-6,7-dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazole and 6,7-dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazole are obtained analogously by reacting 6,6,7-trifluoro-6,7-dihydro-1H-[1,4]dioxino[2,3-f]-benzimidazole-2-thiol, 6-chloro-6,7,7-trifluoro-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazole-2-thiol or 6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazole-2-thiol (respectively) with 2-chloromethyl-4,5-dimethoxypyridinium chloride.

20. 2,2-Difluoro-6-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazole

0.76 g of 2,2-difluoro-6-[(4,5-dimethoxy-2-pyridyl)-methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazole are dissolved in 10 ml of dioxane and 2 ml of 1N sodium hydroxide solution. An equimolar amount of a titrated aqueous sodium hypochlorite solution, to which 1 mole per liter of sodium hydroxide solution has been added, is first added dropwise, while cooling with ice, and after one hour a further equivalent and after 3 hours half the equimolar amount of sodium hypochlorite are added, to achieve complete reaction. After a reaction time of 4 hours, 5 ml of 5% strength sodium thiosulfate solution and another 25 ml of dioxane are added and the upper dioxane phase is separated off, washed once with 5 ml of sodium thiosulfate solution and concentrated on a rotary evaporator. The oily residue is dissolved in 20 ml of water and 10 ml of ethyl acetate and the solution is brought to pH 7 with about 100 ml of a buffer solution of pH 6.8. The solid which has precipitated out is filtered off with suction over a suction filter, washed with water, extracted by stirring at 0° C. with acetone and dried. 0.7 g (87% of theory) of the title compound is obtained in the form of colorless crystals; decomp. at 211°–213° C.

2,2-Difluoro-6-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazole [m.p. 177°–178° C. (decomp.)], 6-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazole, 6,6,7-trifluoro-6,7-dihydro-2-[4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazole, 6-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolol[4,5-f]benzimidazole [m.p. 170°–171° C. (decomp.)], 6-chloro-6,7,7-trifluoro-6,7-dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino-[2,3-f]benzimidazole and 6,7-dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]-benzimidazole are obtained analogously by oxidation of the other sulfides mentioned in Examples 17 to 19 with sodium hypochlorite solution.

21. 2-Mercapto-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole

(a) 55 g of 1-nitro-4-(1,1,2,2-tetrafluoroethoxy)-benzene are hydrogenated in 300 ml of ethanol over 0.5 g of 10% strength palladium-on-charcoal in a circulatory hydrogenation apparatus under atmospheric pressure at 20°–45° C. for 1 hour, the catalyst is filtered off and the solution is concentrated in vacuo at 40° C. The 4-(1,1,2,2-tetrafluoroethoxy)aniline is diluted with 100 ml of glacial acetic acid, 23 ml of acetic anhydride are added dropwise at room temperature, 2 ml of water are added after 30 minutes, the solution is concentrated at 50° C. in vacuo after a short time and 500 ml of icewater are added. 56 g (97% of theoretical) of N-[4-(1,1,2,2-tetrafluoroethoxy)phenyl]-acetamide of m.p. 121°–122° C. are obtained.

(b) 55 g of the above compound are dissolved in 380 ml of dichloromethane, 55 ml of 100% strength nitric acid are added dropwise at room temperature in the course of 10 minutes and the mixture is stirred for a further 6 hours. The organic solution is then washed with aqueous sodium carbonate solution and water, dried with magnesium sulfate and concentrated. 65 g (100% of theoretical) of N-[2-nitro-4-(1,1,2,2-tetrafluoroethoxy)phenyl]-acetamide of m.p. 80°–81° C. (from cyclohexane) are obtained.

(c) 63 g of the above compound are dissolved in 450 ml of methanol, 106 ml of 6M sodium hydroxide solution are added dropwise at room temperature, the mixture is cooled in an ice-bath and 53 g (98% of theoretical) of 2-nitro-4-(1,1,2,2-tetrafluoroethoxy)-aniline (m.p. 85°–86° C.) are precipitated by dropwise addition of 900 ml of water.

(d) 33 g of the above compound are hydrogenated in about 600 ml of isopropanol over 1 g of 10% strength palladium-on-charcoal in a circulatory hydrogenation apparatus under normal pressure at room temperature. The catalyst is filtered off with suction and 34 g (89%) of 4-(1,1,2,2-tetrafluoroethoxy)-1,2-phenylenediamine dihydrochloride of m.p. 275°–276° C. (decomposition) are precipitated with 4M hydrogen chloride in ether.

(e) 330 ml of ethanol, 60 ml of water, 8.9 g of sodium hydroxide and 23 g of potassium o-ethyldithiocarbonate (recrystallized from isopropanol) are added to 33 g of the above compound and the mixture is heated at the boiling point under reflux for 15 hours. 1.2 l of ice-water are added, the pH is brought to 13–14 with sodium hydroxide solution and the mixture is clarified with active charcoal and precipitated with dilute hydrochloric acid to pH 3.5. 27 g (91%) of the title compound of m.p. 316°–319° C. (from isopropanol) are obtained.

22. 2-Mercapto-5-trifluoromethoxy-1H-benzimidazole

The title compound of m.p. 305°–307° C. (decomposition, from toluene) is obtained in 75% yield analogously to Example 21(e) by reaction of 4-trifluoromethoxy-1,2-phenylenediamine dihydrochloride (compare C.A. 55, 23408d, 1961) with potassium O-ethyldithiocarbonate and sodium hydroxide solution in ethanol.

23. 2-Mercapto-5-(2,2,2-trifluoroethoxy)-1H-benzimidazole

(a) 50 g of 1-(2,2,2-trifluoroethoxy)-4-nitrobenzene (*Synthesis* 1980, page 727) are hydrogenated and acetylated analogously to Example 21(a). 50 g (95%) of N-[4-(2,2,2-trifluoroethoxy)phenyl]acetamide (m.p. 140°–141° C.) are obtained.

(b) 42 g of the above compound are stirred with 9.7 ml of 100% strength nitric acid in 290 ml of glacial acetic acid at room temperature for 18 hours and the mixture is precipiated with water. 47 g (94%) of N-[2-nitro-4-(2,2,2-trifluoroethoxy)phenyl]-acetamide (m.p. 117°–118° C.) are obtained.

(c) 47 g of the above compound are hydrolyzed analogously to Example 21(c) to give 38.7 g (97%) of 2-nitro-4-(2,2,2-trifluoroethoxy)-aniline (m.p. 84°–85° C.).

(d) 37 g of the above compound are hydrogenated analogously to Example 21(d) to give 41 g (94%) of 4-(2,2,2-trifluoroethoxy)-1,2-phenylenediamine dihydrochloride of m.p. 230°–233° C. (decomposition).

(e) 30 g (94%) of the title compound (m.p. 288°–290° C.) are obtained analogously to Example 21(e) from 36 g of the above compound.

24. 5-Chlorodifluoromethoxy-2-mercapto-1H-benzimidazole

(a) 10.0 g of N-[4-(chlorodifluoromethoxy)phenyl-]acetamide (m.p. 101°–103° C., from 4-chlorodifluoromethoxyaniline and acetic anhydride) and 12.3 ml of 100% strength nitric acid are stirred in 80 ml of dichloromethane at 20° C. for 4 hours. The mixture is neutralized with aqueous potassium bicarbonate solution and the organic layer is concentrated to give 11.4 g (96%) of N-(4-chlorodifluoromethoxy-2-nitrophenyl)-acetamide (m.p. 89°–91° C.).

(b) 8.6 ml of a 30% strength solution of sodium methylate in methanol are added dropwise to 10.5 g of the above compound in 200 ml of methanol at 5° C., the mixture is stirred for 2 hours, without cooling, ice-water is added and the pH is brought to 8 to give 8.7 g (97%) of 4-chlorodifluoromethoxy-2-nitroaniline (m.p. 40°–42° C.).

(c) 8.5 g of the above compound are hydrogenated over 0.8 g of 10% strength palladium-on-charcoal under normal pressure in 200 ml of methanol, concentrated hydrochloric acid is added, the mixture is filtered, the filtrate is concentrated and the residue is stirred with diisopropyl ether. 8.5 g (97%) of 4-chlorodifluoromethoxy-1,2-phenylenediamine dihydrochloride are obtained.

(d) 6.3 g (72%) of the title compound of m.p. 268°–270° C. (decomposition) are obtained from 8.5 g of the above compound analogously to Example 21(e).

25. 5-Difluoromethoxy-2-mercapto-1H-benzimidazole

(a) 11.8 g of N-(4-difluoromethoxyphenyl)-acetamide [L. M. Jagupol'skii et al., *J. General Chemistry* (USSR) 39, 190 (1969)] are stirred in 200 ml of dichloromethane with 12.1 ml of 100% strength hydrochloric acid at room temperature for 1.5 hours. 13.3 g (92%) of N-[(4-difluoromethoxy-2-nitro)phenyl]-acetamide (m.p. 71°–73° C.) are obtained analogously to Example 21(b).

(b) 4-Difluoromethoxy-2-nitroaniline (m.p. 68°–70° C.) is obtained therefrom in 96% yield analogously to Example 24(b).

(c) 4-Difluoromethoxy-1,2-phenylenediamine dihydrochloride is obtained therefrom in 94% yield analogously to Example 24(c).

(d) The title compound of m.p. 250°–252° C. (from isopropanol) is obtained in 78% yield analogously to Example 24(e).

26. 5,6-Bis(difluoromethoxy)-2-mercapto-1H-benzimidazole

(a) 275 g of chlorodifluoromethane are passed into a solution of 100 g of pyrocatechol, 220 g of sodium hydroxide and 60 g of sodium dithionite in 500 ml of water and 400 ml of dioxane at 50°–55° C. analogously to L. N. Sedova et al., Zh. Org. Khim. 6, 568 (1970). After distillation at 61°–62° C./1.0–1.1 kPa, a mixture of 1,2-bis(difluoromethoxy)benzene and 2-difluoromethoxy-

phenol is obtained, the products being separated by chromatography on silica gel by means of cyclohexane/ethyl acetate (4:1).

(b) A solution of 15 g of 1,2-bis(difluoromethoxy)-benzene and 15 ml of 100% strength nitric acid in 150 ml of dichloromethane is stirred at room temperature for 7 hours. The mixture is neutralized with potassium bicarbonate solution and the organic layer is separated off and chromatographed on silica gel by means of cyclohexane/ethyl acetate (4:1). 1,2-Bis-(Difluoromethoxy)-4-nitro-benzene is obtained. This is hydrogenated and acetylated analogously to Example 21a to give N-[3,4-bis(difluoromethoxy)-phenyl]acetamide (m.p. 81°–83° C.). Analogously to Example 21, furthermore, N-[4,5-bis(difluoromethoxy)-2-nitrophenyl]acetamide (m.p. 65°–67° C.), N-[4,5-bis(difluoromethoxy)-2-nitro]aniline (m.p. 107°–109° C.), 4,5-bis(difluoromethoxy)-1,2-phenylenediamine dihydrochloride and the title compound of m.p. 285°–287° C. (decomposition; from isopropanol) are obtained.

27. 5-Difluoromethoxy-2-mercapto-6-methoxy-1H-benzimidazole

(a) About 58 g of chlorodifluoromethane are passed into a solution of 55.5 g of guaiacol and 130 g of sodium hydroxide in 300 ml of water and 300 ml of dioxane at 60° C. The mixture is filtered at 10° C. and the organic layer is separated off, dried with anhydrous potassium carbonate and distilled. 56 g (73%) of 1-difluoromethoxy-2-methoxybenzene of boiling point 75°–76° C./0.9 kPa are obtained.

(b) A solution of 33.8 ml of 100% strength nitric acid in 90 ml of dichloromethane is added dropwise to a solution of 47 g of the above compound in 230 ml of dichloromethane at 0°–5° C., 250 ml of ice-water are added after 30 minutes and the mixture is neutralized with potassium bicarbonate. The dried organic phase is concentrated in vacuo and the residue is recrystallized from cyclohexane. 53 g (90%) of 1-difluoromethoxy-2-methoxy-5-nitrobenzene (m.p. 45°–49° C.) are obtained. This is hydrogenated and acetylated analogously to Example 21(a). N-(3-Difluoromethoxy-4-methoxyphenyl)acetamide (m.p. 129°–130° C.) is obtained in 90% yield.

(c) 46 g of the above compound are nitrated with 33 ml of 100% strength nitric acid in dichloromethane analogously to the above instructions. N-(5-Difluoromethoxy-4-methoxy-2-nitrophenyl)acetamide (m.p. 116°–117° C.) is obtained in 99% yield.

(d) 54 g of the above compound are stirred in 810 ml of methanol with 44.8 ml of 30% strength methanolic sodium methylate solution at room temperature for 1 hour. The mixture is concentrated in vacuo and ice-water and glacial acetic acid are added to pH 8 to give 5-difluoromethoxy-4-methoxy-2-nitroaniline (m.p. 144°–145° C.) in 99% yield.

(e) 25 g of the above compound are hydrogenated in 300 ml of methanol over 1.25 g of 10% strength palladium-on-charcoal in accordance with Example 21(d). 26 g (88%) of 3-difluoromethoxy-4-methoxy-1,2-phenylenediamine dihydrochloride of m.p. 218°–220° C. (decomposition) are obtained.

(f) 25 g of the above compound are reacted with 19 g of potassium O-ethyldithiocarbonate in accordance with Example 21(e). 20 g (89%) of the title compound of m.p. 280°–282° C. (decomposition; from isopropanol) are obtained.

28. 5-Difluoromethoxy-6-fluoro-2-mercapto-1H-benzimidazole

(a) 1-Difluoromethoxy-2-fluorobenzene (b.p. 76° C./10 kPa $n^{20}/D = 1.4340$) is obtained analogously to Example 27a from 2-fluorophenol and chlorodifluoromethane.

(b) 38.4 ml of 100% strength nitric acid are added dropwise to 30 g of the above compound in 300 ml of dichloromethane at −10° C. and the mixture is stirred at −10° C. for 1 hour and at 0° C. for 2.5 hours. Ice-water is added and the mixture is rendered neutral and chromatographed over silica gel with ethyl acetate/cyclohexane (4:1). 34 g of an oil are obtained, which contains about 90% of 1-difluoromethoxy-2-fluoro-4-nitrobenzene and 10% of 1-difluoromethoxy-2-fluoro-5-nitrobenzene (NMR spectrum).

(c) 30 g of the above mixture are hydrogenated and acetylated analogously to Example 21a. Recrystallization from toluene gives 21 g (65%) of N-(4-difluoromethoxy-3-fluorophenyl)acetamide of m.p. 112°–113° C.

(d) 22.5 ml of 100% strength nitric acid are added dropwise to 20 g of the above compound in 200 ml of dichloromethane at 20° C. in the course of 30 minutes and the mixture is subsequently stirred at room temperature for 15 hours. N-(4-difluoromethoxy-5-fluoro-2-nitrophenyl)acetamide of m.p. 72°–74° C. (from cyclohexane) is obtained in 89% yield analogously to Example 27c. Stirring with 1M hydrochloric acid in methanol at 60° C. for several hours gives 4-difluoromethoxy-5-fluoro-2-nitroaniline of m.p. 95°–97.5° C. in 95% yield and, analogously to Example 27(e), 4-difluoromethoxy-5-fluoro-1,2-phenylene-diamine dihydrochloride in 85% yield. Decomposition from 210° C.

(e) 15 g of the above compound are reacted with 11.8 g of potassium O-ethyldithiocarbonate in accordance with Example 21e. 11.1 g (84%) of the title compound of m.p. 275°–276° C. (decomposition, from isopropanol) are obtained.

29. 2,2-Difluoro-5H-[1,3]-dioxolo[4,5-f]benzimidazole-6-thiol

(a) 30 g of 4-amino-2,2-difluoro-5-nitro-1,3-benzodioxole in 300 ml of methanol are hydrogenated over 0.5 g of 10% strength palladium-on-charcoal in a circulatory hydrogenation apparatus under atmospheric pressure at room temperature, 2.5 equivalents of methanolic hydrogen chloride solution are added, the mixture is filtered, the solution is concentrated in vacuo and isopropanol and ether are added to the residue to give 35 g (97%) of 2,2-difluoro-1,3-benzodioxole-4,5-diamine dihydrochloride of m.p. 232°–233° C. (decomposition).

(b) 24 g of potassium O-ethyldithiocarbonate (recrystallized from isopropanol) and 9.2 of sodium hydroxide in 55 ml of water are added to 30 g of the above compound in 300 ml of ethanol and the mixture is heated to the boiling point under reflux for 15 hours. The mixture is poured onto 1.5 l of water, brought to pH 14 with sodium hydroxide solution, clarified with active charcoal and precipitated with concentrated hydrochloric acid under the influence of heat. The precipitate is filtered off with suction in the cold. 24 g (91%) of the title compound of m.p. 365°–370° C. (decomposition) are obtained.

30. 6,6,7-Trifluoro-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazole-2-thiol

(a) A mixture of 39.5 ml of 69% strength nitric acid and 46 ml of 97% strength sulfuric acid is added dropwise to 50 g of 2,2,3-trifluoro-2,3-dihydro-1,4-benzodioxine at 5° C. in the course of 1 hour. The mixture is stirred at 10° C. for 1 hours, at 20° C. for 1 hour and at 40° C. for 5 minutes, poured onto 200 g of ice and ex-

tracted with dichloromethane. The extract is washed with water, dried with magnesium sulfate and distilled in vacuo. 58 g (94%) of a mixture of 2,2,3-trifluoro-2,3-dihydro-6-nitro- (and 7-nitro)-1,4-benzodioxine of b.p. 68.5° C. (0.15 mbar) and n^{20}/D 1.5080 are obtained. A gas chromatogram with a 10 m fused silica column (Chrompack) shows two peaks in the ratio 2:3.

(b) 35 g of the isomer mixture are hydrogenated in 400 ml of ethanol over 3 g of 10% strength palladium-on-charcoal under atmospheric pressure at 20°–30° C. in a circulatory hydrogenation apparatus, the mixture is filtered and the filtrate is concentrated in vacuo. 30.5 g (100%) of a liquid mixture of 6-amino- (and 7-amino-) 2,2,3-trifluoro-2,3-dihydro-1,4-benzodioxine are obtained.

(c) A mixture of 15.3 g of acetic anhydride and 15 ml of glacial acetic acid is added dropwise to 28 g of the above isomer mixture at 20°–30° C., the mixture is stirred at 30° C. for 30 minutes, 1 ml of water is added, the mixture is stirred at 30° C. for 30 minutes and the solvent is distilled off in vacuo. Recrystallization from toluene gives 19 g of a fraction of a mixture of the isomeric acetamino derivatives of m.p. 128°–133° C.

(d) 14 ml of 100% strength nitric acid, dissolved in 60 ml of dichloromethane, are added dropwise to 17 g of the isomer mixture of the acetamino derivatives, suspended in 100 ml of dichloromethane, at −6° to −8° C. and the mixture is stirred at 0° C. for 2 hours and then at room temperature overnight. The mixture is poured onto 110 g of ice and the organic phase is separated off, washed with water and concentrated in vacuo. The residue (19.8 g) is recrystallized from 20 ml of ethanol. 15.5 g of a mixture of 6-acetamino-2,2,3-trifluoro-2,3-dihydro-7-nitro-1,4-benzodioxine and 7-acetamino-2,2,3-trifluoro-2,3-dihydro-6-nitro-1,4-benzodioxine are obtained.

(e) 14.5 g of the above product mixture are suspended in 80 ml of methanol, and 30 ml of 5M sodium hydroxide solution are added dropwise, while warming to 30° C. The mixture is stirred at room temperature for a further 0.5 hour and poured onto 200 g of ice to give 11.7 g of a mixture of 6-amino-2,2,3-trifluoro-2,3-dihydro-7-nitro-1,4-benzodioxine and 7-amino-2,2,3-trifluoro-2,3-dihydro-6-nitro-1,4-benzodioxine. A sample is separated on a silica gel column with cyclohexane/ethyl acetate (4:1) into two pure isomers of melting points, 110.5°–111.5° C. and 120°–121° C., the NMR spectra of which on a 60 MHz instrument in deuterochloroform are virtually identical.

(f) 10.9 g of the above isomer mixture are hydrogenated in 300 ml of methanol at room temperature under atmospheric pressure over 1 g of 10% strength palladium-on-charcoal in the course of 2.5 hours. 30 ml of 4M hydrogen chloride in methanol are added, the mixture is filtered, the filtrate is concentrated in vacuo and the residue is stirred with 100 ml of ether. 12.6 g (98%) of 2,2,3-trifluoro-2,3-dihydro-1,4-benzodioxine-6,7-diamine dihydrochloride (m.p. 250° C.) are obtained.

(g) 20.5 ml of 4M aqueous potassium hydroxide solution are added to 12 g of the above compound and 8.5 g of potassium O-ethyldithiocarbonate (recrystallized from isopropanol) in 120 ml of ethanol and the mixture is heated to the boiling point under reflux for 17 hours. The mixture is poured onto 300 g of ice, brought to pH 12–13 with potassium hydroxide solution, clarified with active charcoal and precipitated with concentrated hydrochloric acid. Renewed precipitation with acid from alkaline aqueous-alcoholic solution gives 10 g (93%) of the title compound of m.p. 309°–310° C. (decomposition).

31. 6-Chloro-6,7,7-trifluoro-6,7-dihydro-1H-[1,4]dioxino[2,3-f]benzimidazole-2-thiol

(a) A mixture of 18.3 ml of 65% strength nitric acid and 15.4 ml of 97% strength sulfuric acid is added dropwise to 18 g of 2-chloro-2,3,3-trifluoro-2,3-dihydro-1,4-benzodioxine at 5° C. and the mixture is stirred at 5°–10° C. for 2 hours and poured onto ice. It is extracted with methylene chloride to give 21.3 g of a mixture of 2-chloro-2,3,3-trifluoro-2,3-dihydro-6-nitro-(and 7-nitro)-1,4-benzodioxine as an oil.

(b) An oily mixture of 2-chloro-2,3,3-trifluoro-2,3-dihydro-1,4-benzodioxine-6- (and 7-)amine is obtained therefrom in 97% yield analogously to Example 30b, and is reacted quantitatively to give a mixture of the corresponding acetamino derivatives in accordance with Example 30c.

(c) 19 g of the above mixture are stirred in 190 ml of dichloromethane with 16 ml of 100% strength nitric acid and the reaction product is purified by chromatography on silica gel by means of cyclohexane/ethyl acetate (4:1). 15 g of a mixture of 6-acetamino-2-chloro-2,3,3-trifluoro-6,7-dihydro-7-nitro-1,4-benzodioxine and 7-acetamino-2-chloro-2,3,3-trifluoro-6,7-dihydro-6-nitro-1,4-benzodioxine are obtained as a pale yellow oil.

(d) 10.2 ml of a 30% strength solution of sodium methylate in methanol are added dropwise to 14.5 g of the above mixture in 100 ml of methanol at 5° C., the mixture is stirred for 1.5 hours without cooling, poured onto ice, neutralized with dilute hydrochloric acid and extracted with dichloromethane and the extract is concentrated in vacuo. 12.7 g of a mixture of 6-amino-2-chloro-2,3,3-trifluoro-2,3-dihydro-7-nitro-1,4-benzodioxine and 7-amino-2-chloro-2,3,3-dihydro-6-nitro-1,4-benzodioxine are obtained as an orange-colored oil.

(e) 12.4 g of the above mixture are hydrogenated analogously to Example 30f. 12.6 g (99%) of 2-chloro-2,3,3-trifluoro-2,3-dihydro-1,4-benzodioxine-6,7-diamine dihydrochloride are obtained.

(f) 12.4 g of the above compound are reacted with 9.1 g of potassium O-ethyldithiocarbonate and potassium hydroxide solution in ethanol analogously to Example 30g. 9.6 g (74%) of the title compound of m.p. 288°–290° C. (decomposition) are obtained.

32. 2-Chloromethyl-4,5-dimethoxy-pyridinium chloride

(a) Chloromethyl-4,5-dimethoxy-pyridinium chloride

3 ml of thionyl chloride, dissolved in 10 ml of methylene chloride, are added dropwise to a solution, cooled to 0° C., of 5 g of 2-hydroxymethyl-4,5-dimethoxypyridine in 40 ml of methylene chloride in the course of one hour, the reaction mixture is then stirred at 20° C. for 4 hours, during which it becomes red-colored, 5 ml of toluene are added and the mixture is concentrated completely on a rotary evaporator (30° C./5 mbar). The oily residue is dissolved in 50 ml of warm isopropanol and the solution is clarified with a little Tonsil®, filtered and concentration again. The residue is taken up in 10 ml of toluene and the solution is made to crystallize with petroleum ether. After cooling in an ice-bath, the precipitate is filtered off with suction, washed with petroleum ether and dried. 4.6 g (70% of theory) of the title compound 2-chloromethyl-4,5-dimethoxy-pyridinium chloride are obtained as a colorless solid; decomp. at 160°–161° C.

(b) 2-Hydroxymethyl-4,5-dimethoxy-pyridine

19 g of 4,5-dimethoxy-2-methylpyridine 1-oxide are metered into 60 ml of acetic anhydride, warmed to 80°

C., in the course of 30 minutes in a manner such that the temperature does not rise above 100° C. After a further 45 minutes at 85° C., excess acetic anhydride is distilled off in vacuo and the oily dark residue, which essentially consists of the intermediate 2-acetoxymethyl-4,5-dimethoxypyridine is stirred with 80 ml of 2N sodium hydroxide solution at 80° C. for 1 hour. After dilution with 80 ml of water and cooling, the mixture is extracted eight times with 100 ml of methylene chloride each time, the combined organic phases are washed twice with 1N sodium hydroxide solution, dried and concentrated and the crystalline, brownish residue is recrystallized from toluene. 14 g (74% of theory) of 2-hydroxymethyl-4,5-dimethoxy-pyridine of m.p. 122°–124° C. are obtained.

(c) 4,5-Dimethoxy-2-methylpyridine 1-oxide

20 ml of a 30% strength sodium methylate solution are added dropwise to a suspension of 16.9 g of 5-methoxy-2-methyl-4-nitropyridine 1-oxide in 170 ml of dry methanol and the mixture is stirred at 20° C. for 15 hours and then at 50° C. for 4 hours. The pH is brought to 7 by careful addition of concentrated sulfuric acid, while cooling with ice, the mixture is concentrated, the residue is extracted by stirring with 200 ml of methylene chloride, the insoluble constituents are filtered off, 10 ml of toluene are added and the mixture is concentrated to dryness again. 15.2 g (98% of theory) of 4,5-dimethoxy-2-methylpyridine-1-oxide are obtained as colorless crystals of m.p. 118°–121° C.

(d) 5-Methoxy-2-methyl-4-nitropyridine-1-oxide

21.2 g of 5-methoxy-2-methylpyridine 1-oxide are metered into 35 ml of 65% strength nitric acid and warmed to 60° C. in a manner such that the temperature of the reaction mixture does not rise above 80° C. The mixture is stirred at 80° C. for 1 hour, a further 13 ml of 100% strength nitric acid are added to bring the reaction to completion and the mixture is stirred at 60°–70° C. for a further 2 hours. For working up, the mixture is poured onto 300 g of ice. The yellow precipitate which separates out is filtered off over a suction filter, washed with water and dried. The dry solid is boiled up with 200 ml of methylene chloride, filtered off and dried. Further TLC-pure product is isolated by concentration of the filtrate. 22.3 g (87% of theory) of 5-methoxy-2-methyl-4-nitropyridine 1oxide of m.p. 201°–202° C. are obtained as yellow crystals.

(e) 5-Methoxy-2-methylpyridine-1-oxide

120 g of 30% strength hydrogen peroxide solution are added dropwise to a solution of 60.9 g of 5-methoxy-2-methylpyridine in 300 ml of glacial acetic acid at 60° C. in the course of 1 hour and the mixture is subsequently stirred for 3 hours. After destruction of excess per-compounds by addition of active manganese dioxide, the mixture is filtered, the filtrate is concentrated, the residue is clarified hot in 500 ml of ethyl acetate, the mixture is concentrated again and the residue is distilled under 0.3 mbar. 54 g (77% of theory) of 5-methoxy-2-methylpyridine 1-oxide are obtained as a rapidly solidifying oil (b.p. 130° C.); m.p. 80°–84° C.

(f) 5-Methoxy-2-methylpyridine

150 ml of 3-hydroxy-6-methylpyridine are metered into a solution of 84 g of potassium hydroxide in 400 ml of methanol and 500 ml of dimethyl sulfoxide in the course of one hour. After removal of the methanol on a rotary evaporator, 213 g of methyl iodide, dissolved in 100 ml of dimethyl sulfoxide, are added dropwise, while cooling with ice, and the reaction mixture is stirred at 20° C. for 15 hours and subjected to steam distillation. The distillate is extracted continuously in the extractor with methylene chloride and the extract is concentrated. 85 g (56% of theory) of 5-methoxy-2-methylpyridine are obtained as a colorless oil.

33. 2-Chloromethyl-4,5-dimethoxy-3-methylpyridinium chloride

(a) 2-Chloromethyl-4,5-dimethoxy-3-methylpyridinium chloride.

3.45 g (99% of theory) of the title compound are obtained as colorless crystals by the procedure described in Example 32a by reacting 2.7 g of 2-hydroxymethyl-4,5-dimethoxy-3-methylpyridine with 4 g of thionyl chloride in 25 ml of methylene chloride, after a reaction time of 1 hour and after a simplified method of working up characterized by addition of 10 ml of toluene, removal of the methylene chloride and excess thionyl chloride by distillation, removal of the crystals precipitated by filtration with suction and drying; decomp. at 125°–126° C.

(b) 2-Hydroxymethyl-4,5-dimethoxy-3-methylpyridine

4.5 g of 4,5-dimethoxy-2,3-dimethylpyridine 1-oxide are warmed to 110° C. in 20 ml of acetic anhydride in the course of 30 minutes and the mixture is then concentrated on a rotary evaporator. The oily residue, which consists of the intermediate 2-acetoxymethyl-4,5-dimethoxy-3-methylpyridine, is stirred in 30 ml of 3N sodium hydroxide solution at 80° C. for 2 hours, the mixture is extracted, after cooling, five times with 30 ml of methylene chloride each time, the combined organic phases are washed twice with 2N sodium hydroxide solution, dried and concentrated and the residue is stirred with petroleum ether, filtered off with suction and dried. 4.0 g (89% of theory) of 2-hydroxymethyl-4,5-dimethoxy-3-methylpyridine of m.p. 91°–92° C. are obtained.

(c) 4,5-Dimethoxy-2,3-dimethylpyridine 1-oxide

6.3 g of 4,5-dimethoxy-2,3-dimethylpyridine are dissolved in 120 ml of methylene chloride, 20 g of m-chloroperoxybenzoic acid are added successively and the mixture is stirred first at 20° C. for 2 hours and then at 40° C. for 4 hours. After addition of 20 ml of 5N sodium hydroxide solution, the mixture is washed three times with a mixture of 5% strength sodium thiosulfate solution and 5% strength sodium carbonate solution, the aqueous phase is back-extracted twice with methylene chloride and the combined organic phases are dried over magnesium sulfate and concentrated. 4.6 g (66% of theory) of 4,5-dimethoxy-2,3-dimethylpyridine 1-oxide are obtained. The Rf value in methylene chloride/methanol 19:1 is 0.25.

(d) 4,5-Dimethoxy-2,3-dimethylpyridine

7.4 g (74% of theory) of 4,5-dimethoxy-2,3-dimethylpyridine are obtained as a colorless, gradually crystallizing oil of m.p. 36°–38° C. by the procedure described in Example 32f by reaction of 9.18 g of 5-hydroxy-4-methoxy-2,3-dimethylpyridine in 50 ml of dimethyl sulfoxide first with 3.6 g of sodium hydroxide and then with 8.95 g of methyl iodide.

(e) 5-Hydroxy-4-methoxy-2,3-dimethylpyridine

1,000 g of 4-methoxy-2,3dimethylpyridine 1-oxide are metered into 3 l of acetic anhydride at 100° C. in the course of 7 hours while stirring, and the mixture is subsequently stirred at 100° C. for a further 3 hours. The mixture is allowed to cool and is concentrated completely at 70° C./10 mbar and the residue is then distilled under 10^{-2} mbar. The fraction with a boiling range from 95° to 145° C. (mixture of the intermediate 5-acetoxy-4-methoxy-2,3-dimethylpyridine and 2-

acetoxymethyl-4-methoxy-3-methylpyridine) is removed (952 g) and added to 3.5 l of 2N sodium hydroxide solution, warmed to 50° C., in the course of 30 minutes.

The mixture is stirred at 50° C. until a clear solution is formed (about 3 hours), is allowed to cool and is extracted three times with 1 l of methylene chloride each time. The combined organic phases are back-extracted twice with 0.5 l of 1N sodium hydroxide solution each time and the combined aqueous phases are then brought to pH 7.5 with half-concentrated hydrochloric acid, with stirring. The solid which has precipitated out is filtered off, rinsed and dried to constant weight. 5-Hydroxy-4-methoxy-2,3-dimethylpyridine of m.p. 274°–276° C. is obtained.

34. 2-Chloromethyl-3,4-dimethoxy-pyridinium chloride

(a) 2-Chloromethyl-3,4-dimethoxy-pyridinium chloride

4.2 g (93% of theory) of the title compound are obtained as a colorless solid of m.p. 151°–152° C. (decomp.) by the procedure described in Example 32a by reacting 3.38 g of 2-hydroxymethyl-3,4-dimethoxypyridine with 2 ml of thionyl chloride in 30 ml of methylene chloride, after a reaction time of 2.5 hours and after the type of working up described in Example 33a.

(b) 2-Hydroxymethyl-3,4-dimethoxypyridine

After adding 15 ml of 2N sodium hydroxide solution, 4.8 g of 2-acetoxymethyl-3,4-dimethoxypyridine are stirred vigorously at 80° C., whereupon a homogeneous solution forms from the initial two-phase mixture. After 2 hours, the solution is allowed to cool and is extracted five times with 30 ml of methylene chloride each time, the combined organic phases are washed twice with 5 ml of 0.3N sodium hydroxide solution each time, dried over potassium carbonate, filtered and concentrated and the distillation residue is stirred with petroleum ether. 3.6 g (96% of theory) of 2-hydroxymethyl-3,4-dimethoxy-pyridine are obtained as a colorless solid of m.p. 87°–89° C.

(c) 2-Acetoxymethyl-3,4-dimethoxypyridine

4.8 g (28 mmol) of 3,4-dimethoxy-2-methylpyridine 1-oxide are metered into 25 ml of acetic anhydride at 85° C. in the course of one hour, the mixture is stirred at the same temperature for one hour and concentrated completely in vacuo. The brown oily residue is distilled in a bulb tube still under 1 Pa. 5.3 g (90% of theory) of 2-acetoxymethyl-3,4-dimethoxypyridine are obtained; b.p. 125°–130° C.

(d) 3,4-Dimethoxy-2-methylpyridine 1-oxide

4.5 g (25 mmol) of 3-methoxy-2-methyl-4-nitropyridine 1-oxide are stirred at 40° C. in 75 ml of dry methanol, after addition of 4.7 ml of 30% strength sodium methylate solution, for 16 hours. The mixture is then cooled, brought to pH 7 with concentrated sulfuric acid, filtered and concentrated completely in vacuo, the oily, reddish residue is taken up in 50 ml of toluene, the mixture is filtered again to remove insoluble constituents and the filtrate is concentrated to dryness. The yellow oily residue crystallizes on an ice-bath and is finally extracted by stirring with 30 ml of petroleum ether (50/70) at 40° C. filtration and drying in a desiccator gives 5.2 g (88% of theory) of 3,4-dimethoxy-2-methyl-pyridine 1-oxide in the form of pale yellow crystals of m.p. 111°–113° C.

(e) 3-Methoxy-2-methyl-4-nitropyridine 1-oxide

8 ml of concentrated nitric acid are added in four portions of 2 ml each to 5.4 g of 3-methoxy-2-methylpyridine 1-oxide in 12 ml of glacial acetic acid at 80° C. in the course of 6 hours, the mixture is stirred at the same temperature overnight, a further 8 ml of nitric acid are added in three portions in the course of 6 hours and the mixture is stirred for a further 15 hours. After cooling, the mixture is poured onto ice (40 g) and brought to pH 6 with 10N sodium hydroxide solution, the by-product (3-methoxy-2-methyl-4-nitropyridine) which has precipitated out is filtered off and the filtrate is extracted four times with 50 ml of methylene chloride. After drying, the combined organic phases are concentrated completely and the residue is recrystallized from a little methylene chloride/petroleum ether. 4.2 g (57% of theory) of the title compound are obtained in the form of yellow crystals of m.p. 103°–104° C.

(f) 3-Methoxy-2-methylpyridine 1-oxide

15.3 g (0.124 mole) of 3-methoxy-2-methylpyridine are dissolved in 100 ml of glacial acetic acid, and 40 ml of 30% strength hydrogen peroxide are added in 4 portions at 80° C. in the course of 6 hours. The mixture is stirred for a further three hours and then concentrated in vacuo (1.5 kPa), and two 50 ml portions of acetic acid are added, the mixture being concentrated completely after each addition. Following negative detection of per-compounds, the mixture is distilled in a bulb tube oven. The fraction which distills at 120° C. (1.5 Pa) is extracted by stirring in a little diethyl ether and the solid is filtered off and dried. 12 g (60% of theory) of 3-methoxy-2-methylpyridine 1-oxide are obtained in the form of colorless crystals of m.p. 72°–78° C.

(g) 3-Methoxy-2-methylpyridine

15.5 g (90% of theory) of 3-methoxy-2-methylpyridine are obtained as a colorless oil by the procedure described in Example 32f by reaction of 13.7 g (125 mmol) of 3-hydroxy-2-methylpyridine with 9.2 ml of methyl iodide, with the addition of 46 ml of 3M methanolic potassium hydroxide solution and after a reaction time of 3 hours.

COMMERCIAL APPLICABILITY

The dialkoxypyridines of formula I and their pharmacologically-acceptable salts have useful pharmacological properties which render them commercially useful. In particular, they inhibit gastric acid secretion in warm-blooded animals. In addition, they exhibit an excellent protective action on the stomach and intestines of warm-blooded animals. This protective action on the stomach and intestine is observed even upon administering doses below those necessary to inhibit acid secretion. The compounds according to the invention are distinguished by the absence of substantial side effects and by a wide therapeutic range.

The term "protection of the stomach and intestine" comprises the prevention and treatment of gastrointestinal diseases, primarily those which are non-cancerous in origin, especially gastrointestinal inflammatory diseases and lesions (such as, for example, gastric ulcer, duodenal ulcer, gastritis and stomach irritation caused by hyperacidity or medicaments), which can be caused, for example, by microorganisms, bacterial toxins, medicaments (for example certain anti-inflammatories and anti-rheumatics), other chemicals (for example ethanol), gastric acid or stress situations.

Another advantage of the compounds according to the invention is their comparatively high chemical stability.

Surprisingly, the compounds according to the invention are clearly superior (in their excellent properties) to prior art compounds. On the basis of these properties,

the dialkoxypyridines and their pharmacologically-acceptable salts are outstandingly suitable for use in human and veterinary medicine, where they are used, in particular, for the treatment and prophylaxis of diseases of the stomach and intestine and those conditions which result from excessive secretion of gastric juice.

The invention thus also relates to a method for treating mammals suffering from the noted illnesses. The method comprises the administration of a therapeutically and pharmacologically-appropriate amount of one or more of the specified dialkoxypyridines to the sick mammal.

The invention furthermore relates to the compounds according to the invention which are used in this method. The invention moreover relates to the use of the present compounds in the production of medicaments.

The invention also relates to medicaments which contain one or more dialkoxypyridines of formula I and/or their pharmacologically-acceptable salts.

The medicaments are prepared by conventional processes. As medicaments, the pharmacologically-active compounds (=active compounds) according to the invention are used either as such or, preferably, in combination with suitable pharmaceutical auxiliaries, in the form of tablets, coated tablets, capsules, suppositories, plasters (for example as TTS), emulsions, suspensions or solutions, the content of active compound advantageously being between 0.1 and 95%, by weight.

The auxiliaries which are suitable for the desired medicament formulations are known. Solvents, gelling agents, suppository bases, tablets, auxiliaries and other active compound vehicles, as well as antioxidants, dispersing agents, emulsifiers, antifoaming agents, flavor correctants, preservatives, solubilizing agents, colorants or, in particular, permeation promoters and complexing agents (for example cyclodextrins) are useful.

The active compounds are administered orally, parenterally or percutaneously.

In general, it is advantageous in human medicine to administer the active compound or compounds, in the case of oral administration, in a daily dose of from about 0.01 to about 20, preferably 0.05 to 5 and, in particular, 0.1 to 1.5 mg/kg of body weight, if appropriate in the form of several, preferably 1 to 4, individual doses, to achieve the desired result. In the case of parenteral treatment, similar or (especiallly in the case of intravenous administration of the active compound) as a rule lower dosages are effective. The particular optimum dosage and mode of administration of the active compounds required are easily determined by those skilled in the art.

When a compound (and/or a salt thereof) according to the invention is used for treatment of the noted conditions, the pharmaceutical formulation optionally contains one or more pharmacologically-active constituents from other groups of medicaments, such as antacids, for example aluminum hydroxide or magnesium aluminate; tranquilizers, such as benzodiazepines, for example diazepam; spasmolytics, such as bietamiverine and camylofin; anticholinergics, such as oxyphencyclimine and phencarbamide; local anesthetics, such as tetracaine and procaine; and, if appropriate, also enzymes, vitamins or amino acids.

Combination of the compounds according to the invention with other drugs which inhibit acid secretion, such as H_2-blockers (for example cimetidine and ranitidine), and furthermore with so-called peripheral anticholinergics (for example pirenzepine, telenzepine and zolenzepine) and with gastrin antagonists, with the aim of intensifying the main action in the additive or superadditive sense and/or eliminating or reducing side effects, is to be particularly emphasized.

PHARMACOLOGY

The excellent protective action on the stomach and the gastric secretion inhibition shown by the compounds according to the invention is demonstrated in tests using the Shay rat model. The compounds according to the invention investigated appear in the following table:

Serial No.	Name of the compound
1	2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-5-trifluoromethoxy-1H—benzimidazole
2	2-[(4,5-dimethoxy-3-methyl-2-pyridyl)-methylsulfinyl]-5-trifluoromethoxy-1H—benzimidazole
3	2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-5-(1,1,2,2-tetrafluoroethoxy)-1H—benzimidazole
4	2,2-difluoro-6-[(4,5-dimethoxy-2-pyridyl)-methylthio]-5H—[1,3]-dioxolo[4,5-f]benz-imidazole
5	2,2-difluoro-6-[(4,5-dimethoxy-2-pyridyl)-methylsulfinyl]-5H—[1,3]-dioxolo[4,5-f]-benzimidazole

The influence of the compounds investigated on the formation of gastric lesions triggered by pylorus ligature (4 hours; Shay rat) and oral administration of 100 mg/kg of acetylsalicylic acid on the inhibition of gastric secretion (HCl) in rats during 4 hours is shown in the following table:

		Protective Action on the Stomach and Inhibition of Gastric Secretion			
		Protective action on the stomach	Inhibition of the HCl secretion in the stomach (rat; total of 4 hours)		
Serial No.	n [Number of animals]	(rat) inhibition of the lesion index ED50+) [mg/kg, p.o.]	% inhibition of HCl secretion (++)	ED25+ [mg/kg, p.o.]	ED50+ [mg/kg, p.o.]
1	40	0.6	15	1.0	~3
2	48	0.8	25	0.7	1.7
3	56	0.6	18	~1	3.4
4	40	3.5	28	3.0	6.5
5	72	~1	25	1.0	3.0

ED25+ and ED50+ = dose which reduces the lesion index and the HCL secretion (over 4 hours) in the rat stomach by 25% and 50% in the treated group in comparison with the control group.
(++) = after administration of the antiulcerous ED50

The antiulcerogenic action was tested in Shay rats:

Ulcers were provoked in rats which had fasted for 24 hours (female, 180–200 g, 4 animals per cage on a high grid) by pylorus ligature (under diethyl ether anesthesia) and oral administration of 100 mg/10 ml/kg of acetylsalicylic acid. The substances to be tested are administered orally (10 ml/kg) one hour before the pylorus ligature. The wound is closed by means of Michel clamps. 4 hours thereafter, the animals are sacrificed under ether anesthesia by atlas dislocation and the stomach is resected. The stomach is opened longitudinally and fixed to a cork plate, after first determining the amount of secreted gastric juice (volume) and later its HCl content (titration with sodium hydroxide solution). The number and size (=diameter) of ulcers present are determined with a stereomicroscope with 10-

fold magnification. The product of the degree of severity (according to the following points scale) and number of ulcers serves as the individual lesion index.

Point scale:		
no ulcers		0
ulcer diameter	0.1–1.4 mm	1
	1.5–2.4 mm	2
	2.5–3.4 mm	3
	3.5–4.4 mm	4
	4.5–5.4 mm	5
	>5.5 mm	6

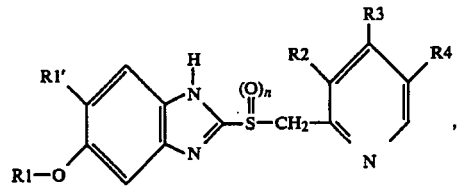
The reduction in the average lesion index of each treated group compared with that of the control group (=100%) serves as a measure of the antiulcerogenic effect. The ED25 and ED50 designate the doses which reduce the average lesion index and the HCL secretion by 25% and 50%.

TOXICITY

The LD50 of all tested compounds is greater than 1,000 mg/kg [p.o] in mice.

What is claimed is:

1. A dialkoxypyridine of formula I



(I)

wherein

R1 is 1–3C-alkyl which is completely or predominantly substituted by fluorine, or chlorodifluoromethyl;

R1' is a hydrogen atom, halo, trifluoromethyl, 1–3C-alkyl, or 1–3C-alkoxy which is unsubstituted or completely or predominatly substituted by fluorine; or

R1 and R1', together with the oxygen atom to which R1 is bonded, is 1–2C-alkylenedioxy which is optionally completely or partly substituted by fluorine, or chlorotrifluoroethylenedioxy;

R3 is 1–3C-alkoxy;

one of R2 and R4 is 1–3C-alkoxy and the other is a hydrogen atom or 1–3C-alkyl; and

n is 0 or 1;

or a salt thereof.

2. A compound according to claim 1 wherein

R1 is 1–3C-alkyl which is completely or predominantly substituted by fluorine, or chlorodifluoromethyl;

R1' is a hydrogen atom, halo, trifluoromethyl, 1–3C-alkyl, or 1–3C-alkoxy which is unsubstituted or completely or predominantly substituted by fluorine;

R3 is 1–3C-alkoxy;

one of R2 and R4 is 1–3C-alkoxy and the other is a hydrogen atom or 1–3C-alkyl; and

n is 0 or 1, or a salt thereof.

3. A compound according to claim 1 wherein,

R1 and R1', together with the oxygen atom to which R1 is bonded, is 1–2C-alkylenedioxy which is unsubstituted or completely or partly substituted by fluorine, or chlorotrifluoroethylenedioxy,

R3 is 1–3C-alkoxy;

one of R2 and R4 is 1–3C-alkoxy and the other is a hydrogen atom or a 1–3C-alkyl radical and n is 0 or 1, or a salt thereof.

4. A compound according to claim 2, wherein R1' is a hydrogen atom and R1, R2, R3, and R4 and n have their previously-ascribed meanings, or a salt thereof.

5. A compound according to claim 2 wherein R1 is 1,1,2,2-tetrafluoroethyl, trifluoromethyl, 2,2,2-trifluoroethyl, difluoromethyl or chlorodifluoromethyl, R1' is a hydrogen atom, R3 is methoxy, one of R2 and R4 is methoxy and the other is a hydrogen atom or methyl and n is 0 or 1, or a salt thereof.

6. A compound according to claim 2, wherein R1 is 1,1,2,2-tetrafluoroethyl, trifluoromethyl, 2,2,2-trifluoroethyl or difluoromethyl, R1' is a hydrogen atom, R3 is methoxy, one of R2 and R4 is methoxy and the other is a hydrogen atom or methyl and n is 0 or 1, or a salt thereof.

7. A compound according to claim 4, 5, or 6, wherein R2 is a hydrogen atom or methyl and R3 and R4 are methoxy, or a salt thereof.

8. A compound according to claim 4, 5 or 6, wherein R4 is a hydrogen atom and R2 and R3 are methoxy, or a salt thereof.

9. A compound according to claim 3, wherein R1 and R1', together with the oxygen atom to which R1 is bonded, are 1–2C-alkylenedioxy, and R2, R3, R4 and n have the meanings given in claim 3, or a salt thereof.

10. A compound according to claim 3, wherein R1 and R1', together with the oxygen atom to which R1 is bonded, are methylenedioxy or ethylenedioxy, and R2, R3, R4 and n have the meanings given in claim 3, or a salt thereof.

11. A compound according to claim 3, wherein R1 and R1', together with the oxygen atom to which R1 is bonded, are 1–2C-alkylenedioxy which is completely or partly substituted by fluorine and R2, R3, R4 and n have the meanings given in claim 3, or a salt thereof.

12. A compound according to claim 3, wherein R1 and R1', together with the oxygen atom to which R1 is bonded, are difluoromethylenedioxy or 1,1,2-trifluoroethylenedioxy and R2, R3, R4 and n have the meanings given in claim 3, or a salt thereof.

13. A compound according to claim 3 wherein R1 and R1', together with the oxygen atom to which R1 is bonded, are difluoromethylenedioxy or methylenedioxy and R2, R3, R4 and n have the meanings given in claim 3, or a salt thereof.

14. A compound according to claims 9, 10, 11, 12 or 13, wherein R2 is a hydrogen atom or methyl, R3 is methoxy, R4 is methoxy, or a salt thereof.

15. A compound according to claims 9, 10, 11, 12 or 13, wherein R2 is methoxy, R3 is methoxy, and R4 is a hydrogen atom or methyl, or a salt thereof.

16. A compound according to claims 9, 10, 11, 12, or 13, wherein R2 is methoxy, R3 is methoxy and R4 is methyl, or a salt thereof.

17. A compound according to claim 1, wherein n is 0, or an acid addition salt thereof.

18. A compound according to claim 1, wherein n is 1, or a salt thereof with a base.

19. A compound according to claim 1 selected from the group consisting of 2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-5-trifluoromethoxy-1H-benzimidazole, 2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-5-trifluoromethoxy-1H-benzimidazole, 2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole, 2,2-difluoro-6-[(4,5-dimethoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazole and 2,2-difluoro-6-[(4,5-dimethoxy-2-

pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazole, or a salt thereof.

20. A pharmaceutically-acceptable compound which is a dialkoxypyridine according to claim 1 or a salt thereof.

21. A compound according to claim 1 which is 2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole or a pharmacologically-compatible salt thereof.

22. A compound according to claim 1 which is 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole or a pharmacologically-compatible salt thereof.

23. A compound according to claim 1 wherein R1 is difluoromethyl, 1,1,2,2-tetrafluoroethyl or 2,2,2-trifluoroethyl; R1' is a hydrogen atom or methoxy; or R1 and R1', together with the oxygen atom to which R1 is bound, is difluoromethylenedioxy or 1,1,2-trifluoroethylenedioxy; R3 is methoxy; one of R2 and R4 is methoxy, and the other is hydrogen; and n is 0 or 1; or a salt thereof.

24. A compound according to claim 1 wherein R1 is difluoromethyl, 1,1,2,2-tetrafluoroethyl or 2,2,2-trifluoroethyl; R1' is a hydrogen atom; R3 is methoxy; one of R2 and R4 is methoxy, and the other is hydrogen; and n is 0 or 1; or a salt thereof.

25. The compound according to claim 1 which is 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole sodium salt.

26. A medicament composition useful to inhibit gastric acid secretion in and to protect the stomach and intestines of warm-blooded animals and comprising an active ingredient and a pharmaceutical auxiliary, the active ingredient comprising from 0.1 to 95 percent by weight of at least one pharmaceutically-acceptable compound according to claim 20.

27. A method for treatment or prophylaxis of illness based on excessive secretion of hydrochloric acid by the stomach which comprises administering an effective amount of a compound according to claim 20 to a mammal suffering from said illness.

28. A method for providing protective action for the stomach and intestines which comprises administering an effective amount of a compound according to claim 20 to a mammal.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,758,579

DATED : July 19, 1988

INVENTOR(S) : Bernhard KOHL; Ernst STURM; Georg RAINER

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 2, line 58, "1,1,2,2L" should read --1,1,2,2--. Column 3, line 40, "alkylenedioxyradical" should read --alkylenedioxy radical--; line 61, "represent" should read --represents--. Column 8, line 10, "4,5-d" should read --4,5-f--. Column 16, line 67, "Example 'by" should read --Example 1 by--. Column 22, line 47, "hydrochloric" should read --nitric--; line 59, "24" should read --21--. Column 24, line 67, "hours," should read --hour,--. Column 26, line 58, "concentration" should read --concentrated--. Column 27, line 45, "loxide" should read --1-oxide--. Column 29, line 61, "filtration" should read --Filtration--.

Signed and Sealed this

Fourth Day of July, 1989

Attest:

Attesting Officer

DONALD J. QUIGG

Commissioner of Patents and Trademarks

D

Patent Maintenance Fees - Public Inquiry

Patent#: 4758579 Filed: 04/28/87 Issued: 07/19/88 Serial#: 07045799
Status: 4th, 8th And 12th Year Fees Paid Sml Entity: NO
Window Opens: Surchg Due: Expiration:
Fee Amt Due:$ Surchg Amt Due:$ Total Amt Due:$
Fee Code: Surchg Code:
Title: FLUOROALKOXY SUBSTITUED BENZIMIDAZOLES USEFUL AS GASTRIC ACID SECRETION INHIBITORS

Address For Fee Purposes:
BERMAN, AISENBERG & PLATT
1730 RHODE ISLAND AVE., N.W.
WASHINGTON DC 20036-3186

Most Recent Significant Events:

12/20/99	Payment of Maintenance Fee, 12th Year, Large Entity
12/12/95	Payment of Maintenance Fee, 8th Year, Large Entity
12/09/91	Payment of Maintenance Fee, 4th Year, PL 97-247
12/09/91	Last Event On Maintenance History

E

IND No. 35,441
Pantoprazole Tablets
Chronology of FDA Correspondences

Date of Submission	Description
September 13, 1990	Original IND No. 35,441 submitted
September 25, 1990	FDA letter acknowledging IND submission and assigning IND No. 35,441
October 11, 1990	FDA telephone contact conveying that clinical study could not be initiated due to deficiencies.
November 1, 1990	FDA letter placing IND on clinical hold
December 19, 1990	Response to 11/1/90 FDA letter
January 9, 1991	FDA letter acknowledging status of IND review
February 13, 1991	Response to 1/9/91 FDA letter
February 20, 1991	FDA preclinical meeting
November 27, 1991	Informed FDA of SB's intention not to conduct clinical trials
October 21, 1992	Transfer of IND to Byk Gulden (BG), represented by Altana, Inc.
October 20, 1993	Submission of additional preclinical and clinical information
November 4, 1993	FDA request for supplementary data on carcinogenicity studies
January 10, 1994	Response to letter of 11/4/93
February 1, 1995	Submission of independent expert report
June 5, 1996	Transfer of IND sponsorship to Wyeth-Ayerst
June 7, 1996	Request for release of clinical hold
September 4, 1996	General Correspondence: End of Phase II meeting proposal of clinical development plan
October 8, 1996	End of Phase II meeting
October 15, 1996	FDA letter received regarding release of clinical hold and initiation of acute studies
October 30, 1996	Submission of New Protocols
December 13, 1996	Release of FDA clinical hold
August 8, 1997	Request for pre-NDA meeting
October 15, 1997	Pre-NDA meeting
February 11, 1998	Request for NDA electronic regulatory submission (ERS) meeting
February 20, 1998	Annual Report
March 30, 1998	NDA ERS meeting
April 3, 1998	FDA teleconference to discuss NDA submission

IND No. 35,441
Pantoprazole Tablets
Chronology of FDA Correspondences

Date of Submission	Description
June 16, 1998	Response to 5/22/98 FDA correspondence
July 8, 1998	FDA request for clinical information
September 4, 1998	FDA letter concerning IB preclinical section
September 22, 1998	Response to 7/8/98 FDA request for clinical information
November 24, 1998	Response to 9/1/98 FDA request (to NDA 20-987) for information
December 30, 1998	Pharmacology/Toxicology submission
January 28, 1999	Annual Report
June 7, 1999	Proposed Pediatric Study Request
Jan. 31, 2000	IND Annual Report
Jan. 31, 2000	Proposed Pediatric Study Request

F

PATENT
Atty. Docket No.: 1142.0121

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No. 4,758,579)
)
Issued: July 19, 1988)
)
To: Bernhard Kohl, Ernst Sturm,)
Georg Rainer)
)
Assignee: BYK Gulden Lomberg Chemische)
Fabrik GmbH)
)
For: FLUOROALKOXY SUBSTITUTED)
BENZIMIDAZOLES USEFUL AS)
GASTRIC ACID SECRETION)
INHIBITORS)

ATTN: BOX PATENT EXTENSION
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

CERTIFICATION

I, CHARLES E. VAN HORN, do hereby certify that this accompanying application for extension of the term of U.S. Patent 4,758,579 under 35 U.S.C. § 156 including its attachments and supporting papers is being submitted as one original and four (4) copies thereof.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

By: Charles E. Van Horn
Charles E. Van Horn
Reg. No. 40,266

Date: March 28, 2000

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& DUNNER, L.L.P.
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WASHINGTON, D. C. 20005
202-408-4000

PATENT
Atty. Docket No.: 1142.0121

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No. 4,758,579)
)
Issued: July 19, 1988)
)
To: Bernhard Kohl et al.)
)
For: FLUOROALKOXY SUBSTITUTED)
BENZIMIDAZOLES USEFUL AS)
GASTRIC ACID SECRETION)
INHIBITORS)

ATTN: BOX PATENT EXTENSION
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

DECLARATION ACCOMPANYING APPLICATION UNDER 35 U.S.C. § 156 FOR EXTENSION OF PATENT TERM

I, CHARLES E. VAN HORN, do hereby declare:

I am a patent attorney authorized to practice before the United States Patent and Trademark Office and I have been appointed as an attorney by the Patent Assignee, BYK Gulden Lomberg Chemische Fabrik GmbH, with regard to this application for extension of the term of U.S. Patent 4,758,579 and to transact all business in the U.S. Patent and Trademark Office in connection therewith.

I have reviewed and understand the contents of the accompanying application being submitted pursuant to 37 C.F.R. § 1.740.

I believe that the patent is subject to extension pursuant to 37 C.F.R. § 1.710.

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WASHINGTON, D. C. 20005
202-408-4000

I believe an extension of the length claimed is justified under 35 U.S.C. § 156 and applicable regulations.

I believe the patent for which the extension is being sought meets the conditions for extension of the term of a patent as set forth in 37 C.F.R. § 1.720.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

By: Charles E Van Horn

Charles E. Van Horn
Reg. No. 40,266

Date: March 28, 2000

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